Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/006022

International filing date: 24 February 2005 (24.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/547,543
Filing date: 25 February 2004 (25.02.2004)

Date of receipt at the International Bureau: 31 March 2005 (31.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1296657

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 16, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/547,543***
FILING DATE: ***February 25, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/06022***

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

16569 U.S. PTO
022504

"EXPRESS MAIL CERTIFICATE"

"Express Mail" Mailing Label Number EV 332 946 535 US

Date Of Deposit: 24 February 2004

I Hereby Certify That This Paper Or Fee Is Being Deposited With The United States Postal Service "Express Mail Post Office To Addressee" Service Under 37 CFR 1.10 On The Date Indicated Above And Is Addressed To: COMMISSIONER FOR PATENTS, MAIL STOP: PROVISIONAL APPLICATION, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450

Name Of Person Mailing Paper Or Fee

(Type Or Print) Aron Graham

Signature Aaron Graham

22264 U.S. PTO
60/547543
022504

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	TC00009P

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
JOHNSON	Neil	W.	Downingtown, Pennsylvania
GOODMAN	Stephen	N.	Wayne, Pennsylvania
KASPAREC	Jiri		Collegeville, Pennsylvania
HASEGAWA	Masaichi		Ibaraki, Japan

TITLE OF THE INVENTION (280 characters max)

Novel Chemical Compounds

Correspondence Address:
GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5009
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-0939	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	68	**Total Number of Pages = 69**
☒ Abstract	Number of Pages	1	
☐ Drawings	Number of Sheets		☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$160.00**

Respectfully submitted,
Signature: Elizabeth J. Hecht
Elizabeth J. Hecht

Date: 24 February 2004
Registration No.: **41,824**

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Commissioner for Patents, P.O. Box 1450, Mail Stop: Patent Application, Alexandria, VA 22313-1450.

20462
CUSTOMER NUMBER

N:\HAN\APPS\TC00009P\provtransmittal.doc

Novel Chemical Compounds

FIELD OF THE INVENTION

This invention relates to newly identified compounds for inhibiting hYAK3 proteins and methods for treating diseases associated with the imbalance or inappropriate activity of hYAK3 proteins.

BACKGROUND OF THE INVENTION

A number of polypeptide growth factors and hormones mediate their cellular effects through a signal transduction pathway. Transduction of signals from the cell surface receptors for these ligands to intracellular effectors frequently involves phosphorylation or dephosphorylation of specific protein substrates by regulatory protein serine/threonine kinases (PSTK) and phosphatases. Serine/threonine phosphorylation is a major mediator of signal transduction in multicellular organisms. Receptor-bound, membrane-bound and intracellular PSTKs regulate cell proliferation, cell differentiation and signalling processes in many cell types.

Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, many cancers and other proliferative diseases. Accordingly, serine/threonine kinases and the signal transduction pathways which they are part of are potential targets for drug design.

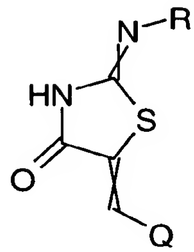
A subset of PSTKs are involved in regulation of cell cycling. These are the cyclin-dependent kinases or CDKs (Peter and Herskowitz, Cell 1994: 79, 181-184). CDKs are activated by binding to regulatory proteins called cyclins and control passage of the cell through specific cell cycle checkpoints. For example, CDK2 complexed with cyclin E allows cells to progress through the G1 to S phase transition. The complexes of CDKs and cyclins are subject to inhibition by low molecular weight proteins such as p16 (Serrano et al, Nature 1993: 366, 704), which binds to and inhibits CDK4. Deletions or mutations in p16 have been implicated in a variety of tumors (Kamb et al, Science 1994: 264, 436-440). Therefore, the proliferative state of cells and diseases associated with this state are dependent on the activity of CDKs and their associated regulatory molecules. In diseases such as cancer where inhibition of proliferation is desired, compounds that inhibit CDKs may be useful therapeutic agents. Conversely, activators of CDKs may be useful where enhancement of proliferation is needed, such as in the treatment of immunodeficiency.

YAK1, a PSTK with sequence homology to CDKs, was originally identified in yeast as a mediator of cell cycle arrest caused by inactivation of the cAMP-dependent protein kinase PKA (Garrett et al, Mol Cell Biol. 1991: 11-6045-4052). YAK1 kinase activity is low in cycling yeast but increases dramatically when the cells are arrested prior to the S-G2 transition. Increased expression of YAK1 causes growth arrest in yeast cells deficient in PKA. Therefore, YAK1 can act as a cell cycle suppressor in yeast.

Our US patent no. 6,323,318 describes two novel human homologs of yeast YAK1 termed hYAK3-2, one protein longer than the other by 20 amino acids. hYAK3-2 proteins (otherwise reported as REDK-L and REDK-S in *Blood*, 1 May 2000, Vol 95, No. 9, pp2838) are primarily localized in the nucleus. hYAK-2 proteins (hereinafter simply referred as hYAK3 or hYAK3 proteins) are present in hematopoietic tissues, such as bone marrow and fetal liver, but the RNA is expressed at significant levels only in erythroid or erthropoietin (EPO)-responsive cells. Two forms of REDK cDNAs appear to be alternative splice products. Antisense REDK oligonucleotides promote erythroid colony formation by human bone marrow cells, without affecting colony-forming unit (CFU)-GM, CFU-G, or CFU-GEMM numbers. Maximal numbers of CFU-E and burst-forming unit-erythroid were increased, and CFU-E displayed increased sensitivity to suboptimal EPO concentrations. The data indicate that REDK acts as a brake to retard erythropoiesis. Thus inhibitors of hYAK3 proteins are expected to stimulate proliferation of cells in which it is expressed. More particularly, inhibitors of hYAK3 proteins are useful to treat or prevent diseases of the erythroid and hematopoietic systems mediated the imbalance or inappropriate activity of hYAK3 proteins, including but not limited to, anemias due to renal insufficiency or to chronic disease, such as autoimmunity, HIV, or cancer, and drug-induced anemias, myelodysplastic syndrome, aplastic anemia and myelosuppression, and cytopenia.

SUMMARY OF THE INVENTION

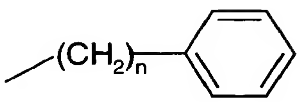
In the first aspect, the present invention relates to a compound of the formula I, or a salt, solvate, or a physiologically functional derivative thereof



I

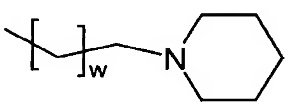
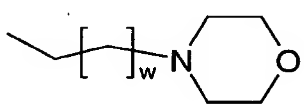
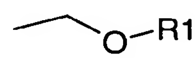
in which

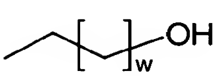
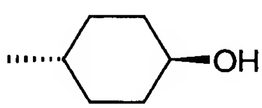
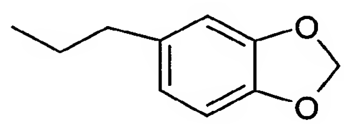
R is

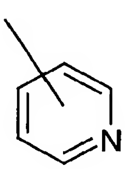
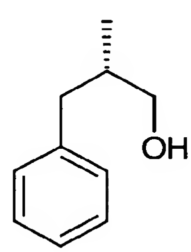


in which the phenyl radical is optionally and independently substituted with up to three halogen, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-CF_3$, $-CN$, $-CO_2H$, $-SO_2NH_2$, $-CONH_2$; or

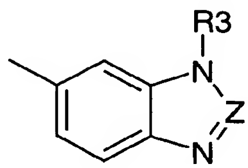
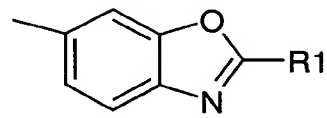
R is a radical of the formula

 ,  ,  ,

 ,  , 

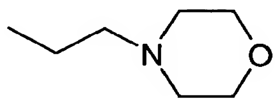
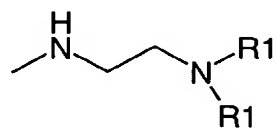
 ,  ; and

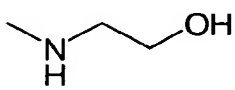
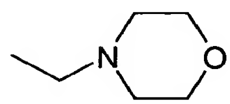
Q is a radical of the formula

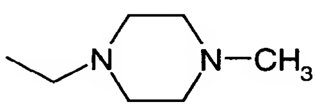
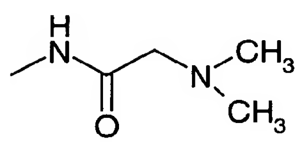
 or 

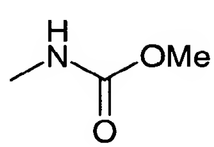
in which Z is N or C-R2;

wherein R2 is hydrogen, $-NH_2$, $-C_{1-6}$alkyl, $-CF_3$, or a radical of the formula

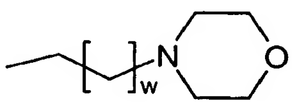
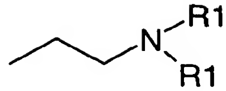
 ,  ,

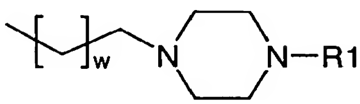
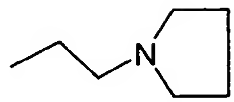
 ,  ,

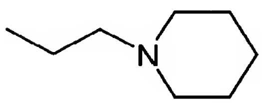
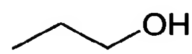
 ,  , or

 ; and

R3 is $-C_{1-6}$ alkyl, or a radical of the formula

 ,  ,

 ,  ,

 , or  ; and

n equals zero to two;
w equals one to two; and
R1 is $-C_{1-6}$alkyl.

In a second aspect, the instant invention relates a method of inhibiting hYAK3 in a mammal; comprising, administering to the mammal a therapeutically effective amount of a compound of the formula I, or a salt, solvate, or a physiologically functional derivative thereof.

In a third aspect of the present invention, there is provided a pharmaceutical composition including a therapeutically effective amount of a compound of formula I, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a fourth aspect of the present invention, there is provided the use of a compound of formula I, or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment or prevention of a disorder of the erythroid and hematopoietic systems mediated by the imbalance or inappropriate activity of hYAK3 proteins, including but not limited to, anemias due to renal insufficiency or to chronic disease, such as autoimmunity, HIV, or cancer, and drug-induced anemias, myelodysplastic syndrome, aplastic anemia and myelosuppression, and cytopenia.

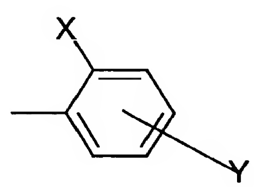
In a fifth aspect, the present invention relates to a method of treating or preventing diseases of the erythroid and hematopoietic systems, caused by the hYAK3 imbalance or inappropriate activity including, but not limited to, anemias due to renal insufficiency or to chronic disease, such as autoimmunity, HIV, or cancer, and drug-induced anemias, myelodysplastic syndrome, aplastic anemia and myelosuppression, and cytopenia; comprising, administering to a mammal a therapeutically effective amount of a compound of formula I, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

In a six aspect, the present invention relates to a method of treating or preventing anemias due to renal insufficiency or to chronic disease, such as autoimmunity, HIV, or cancer, and drug-induced anemias, myelodysplastic syndrome, aplastic anemia and myelosuppression, and cytopenia; comprising, administering to a mammal a therapeutically effective amount of a compound of formula I, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients..

DETAILED DESCRIPTION

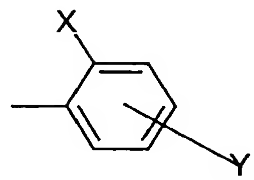
A preferred compound of formula I is in which R is phenyl optionally and independently substituted with up to three halogen, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-CF_3$, -CN, $-CO_2H$, $-SO_2NH_2$, -$CONH_2$.

In a more preferred embodiment, a compound of formula I has R defined as a radical of the formula

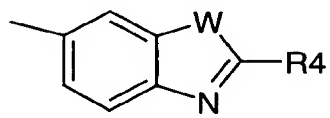


in which X is halogen or CF3; and Y is hydrogen, halogen, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-CF_3$, -CN, $-CO_2H$, $-SO_2NH_2$, $-CONH_2$.

Yet, in a more preferred embodiment, a compound of formula I has R defined as a radical of the formula



in which X is halogen or -CF3; and Y is hydrogen, halogen, -C_{1-6}alkyl, -OC_{1-6}alkyl, -CF_3, -CN, -CO_2H, -SO_2NH_2, -$CONH_2$; and Q is



in which R4 is methyl or hydrogen, and W is O or N-R1, in which R1 is -C_{1-6}alkyl.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon. Furthermore, as used herein, the term "C_{1-6} alkyl" refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C_{1-6} alkyl" groups useful in the present invention include methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl,t-butyl, n-pentyl, n-hexyl, and the like.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

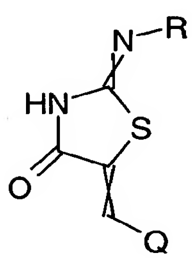
As used herein, the term "C_{3-6} cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to six carbon atoms. Exemplary "C_{3-6} cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "optionally" means that the subsequently described event(s) may or

may not occur, and includes both event(s), which occur, and events that do not occur.

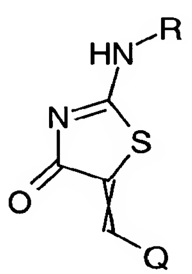
As used herein, the crisscrossed double bond indicated by the symbol "  " denotes Z and/or E stereochemistry around the double bond. In other words a compound of formula I can be either in the Z or E stereochemistry around this double bond, or a compound of formula I can also be in a mixture of Z and E stereochemistry around the double bond. However, in formula I, the preferred compounds have Z stereochemistry around the double bond to which radical Q is attached.

A compound of formula I naturally may exist in one tautomeric form or in a mixture of tautomeric forms. For example, for sake simplicity, a compound of formula I is expressed in one tautomeric form, usually as an exo form, i.e.



Exo form

However, a person of ordinary skill can readily appreciate the compounds of formula I can also exist in endo forms.



Endo form

The present invention contemplates all possible tautomeric forms.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers, or two or more diastereoisomers. Accordingly, the compounds of this invention include mixtures of enantiomers/diastereoisomers as well as purified enantiomers/diastereoisomers or enantiomerically/diastereoisomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula I above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, as stated above, it is understood that all tautomers and mixtures of tautomers are included within the scope of the compounds of formula I.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in the compound of formula I. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

While it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula I, as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions (otherwise referred to as pharmaceutical formulations), which include therapeutically effective amounts of compounds of the formula I and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula I and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula I, or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a

predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of the formula I, depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula I, and salts, solvates and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula I, and salts, solvates and physiological functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an

ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example

water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula I for the treatment of or prevention of diseases of the erythroid and hematopoietic systems, caused by hYAK3 imbalance or inappropriate activity including, but not limited to, neutropenia; cytopenia; anemias, including anemias due to renal insufficiency or to a chronic disease, such as autoimmunity, HIV or cancer, and drug-induced anemias; and myelosuppression will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula I per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

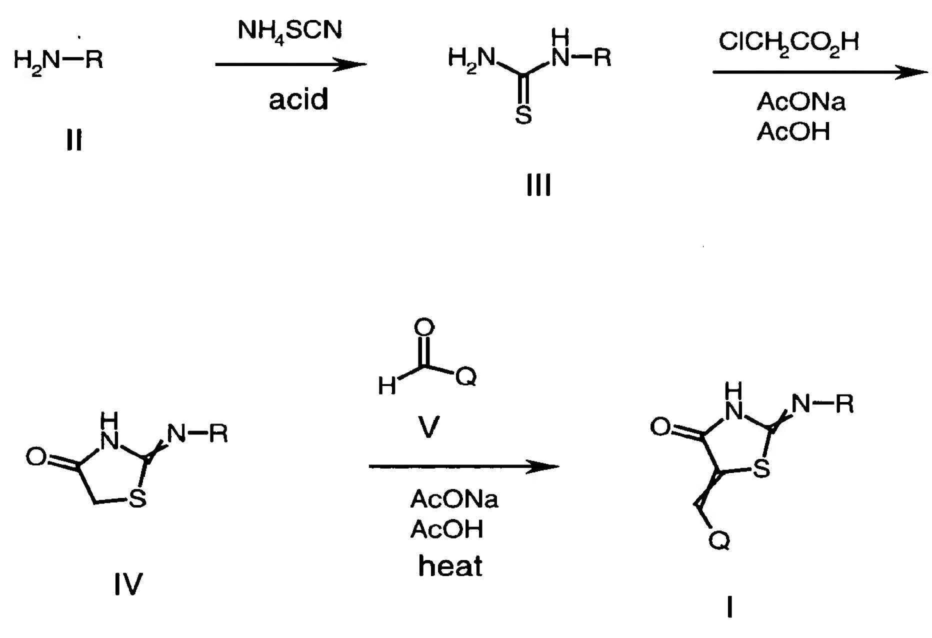
Method of Preparation

Compounds of general formula I may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley &

Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula I. Those skilled in the art will recognize if a stereocenter exists in compounds of formula I. Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

More particularly, the compounds of the formula I can be made by the process of either Scheme A or B or a variant thereof. Any person skilled in the art can readily adapt the process of either A or B, such the stoichemistry of the reagents, temperature, solvents, etc. to optimize the yield of the products desired.

Scheme A



Briefly in Scheme A, a mixture of aniline derivative of formula II (1 equivalent) and NH4SCN (about 1.3 equivalent) in an acid (typically 4N-HCl) is heated to reflux at about

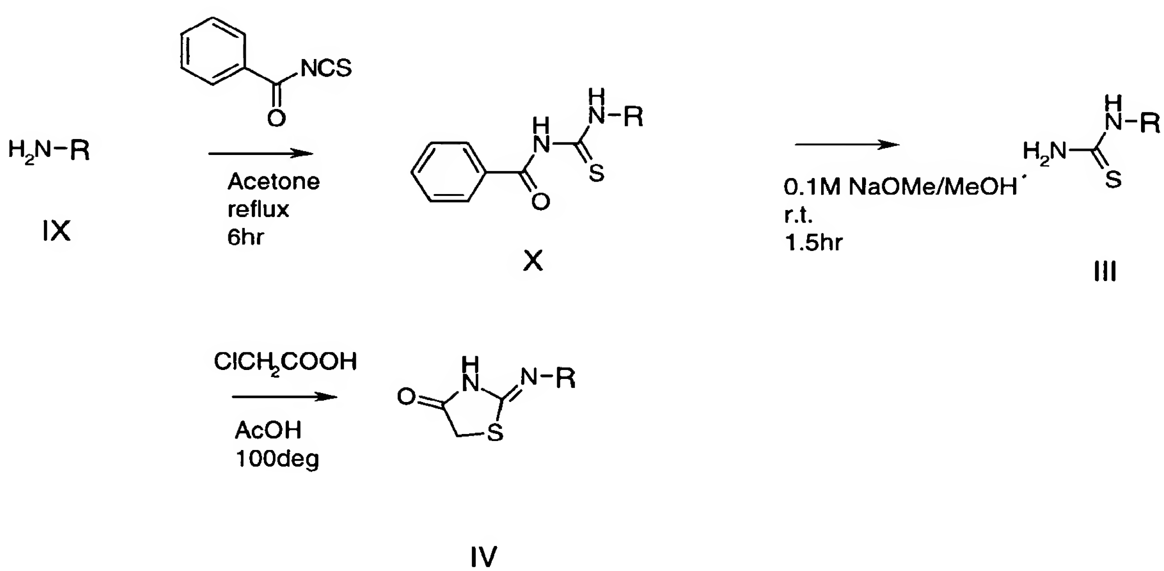
110 C° for 6 hours. After cooling, the mixture is treated with H_2O, which process usually forms a solid, followed by desiccation *in vacuo* to give a compound of formula III. (However, the compounds of formula III are often commercially available.)

A mixture of formula III compound, $ClCH_2CO_2H$ (1 equivalent), and AcONa (1 equivalent) in AcOH is heated to reflux at around 110 C° for about 4 h. The mixture is poured onto water thereby a solid is typically formed, which is isolated by filtration. The solid is washed with a solvent such as MeOH to afford a compound of formula IV.

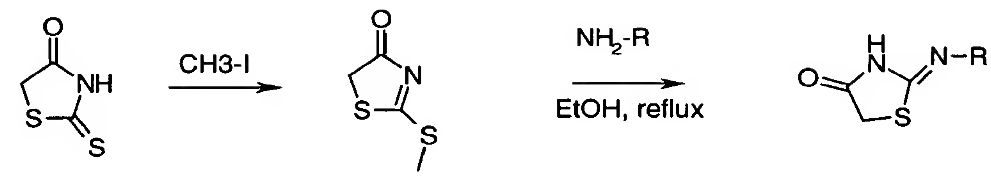
A mixture of formula IV compound, an aldehyde of formula V (1 equivalent), AcONa (3 equivalent) in AcOH is heated to reflux at about 110 C° for about 10 to 48 hours. After cooling, a small portion of water was added until the solid forms. The solid is filtered and washed with a solvent such as MeOH, followed by desiccation *in vacuo* to afford a target product of formula I.

As a variation of Scheme A, a compound of formula IV can also be synthesized according to Scheme A' or Scheme A".

Scheme A'



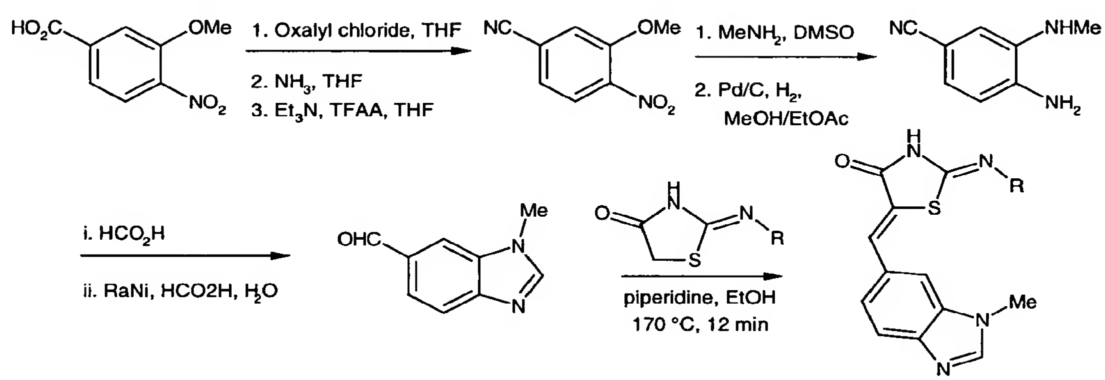
Scheme A"



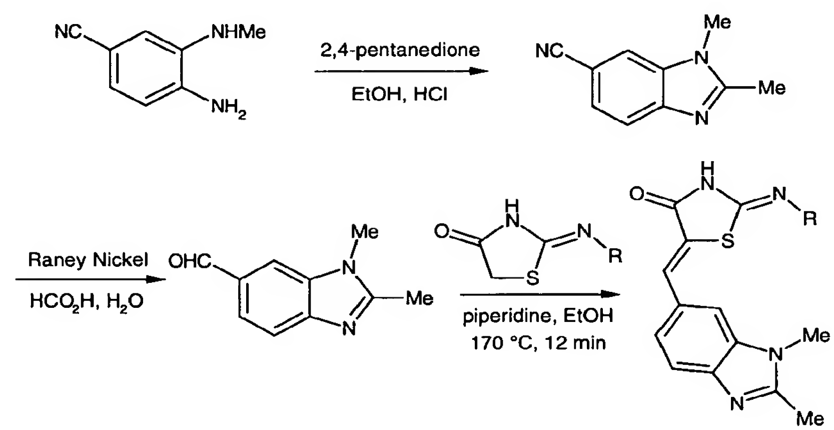
IV

Compounds of formula V are known or can be made by standard organic chemical techniques. For exampl, Schemes 1 to 9 depict some of the ways to make a compound of formula V, and further ways to make a compound of formula I from a compound of formula V.

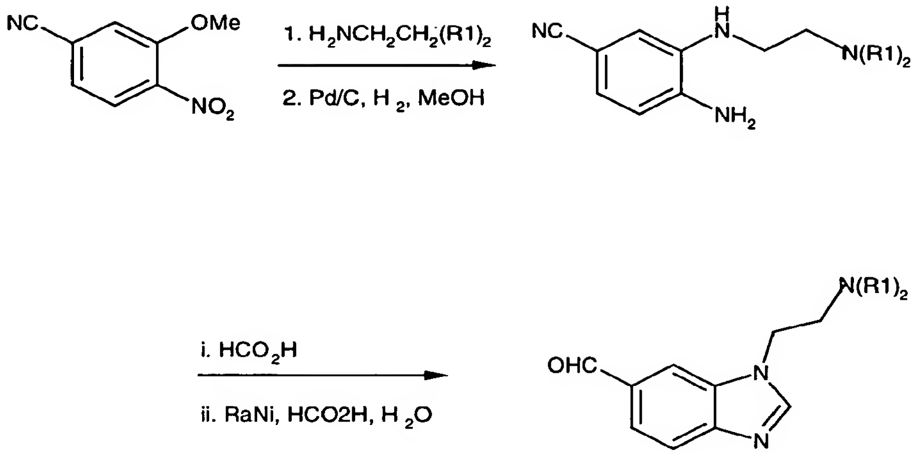
Scheme 1. 1-Methylbenzimidazoles



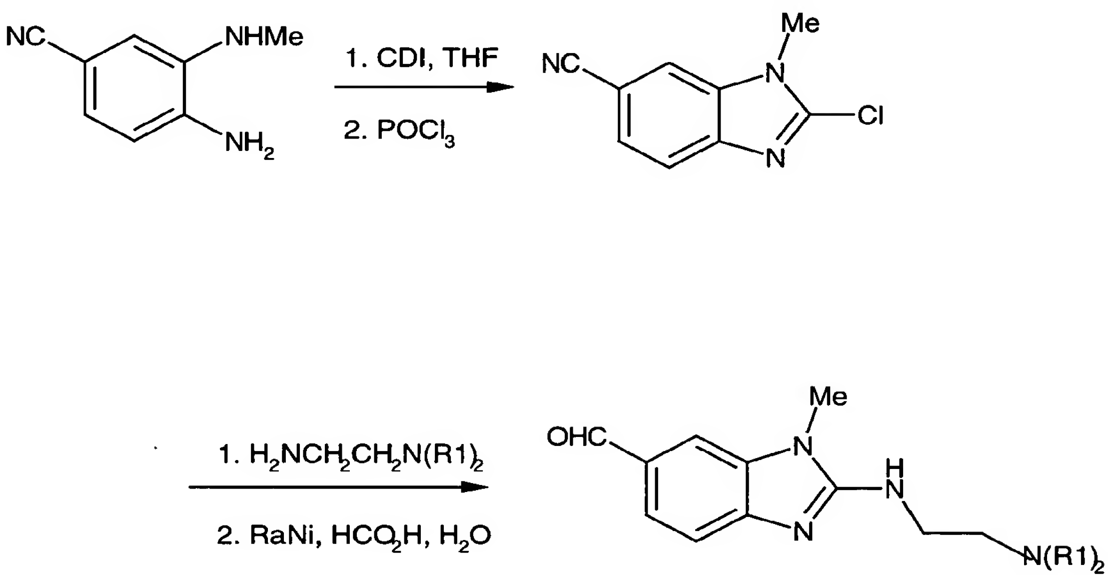
Scheme 2. 1,2-Dimethylbenzimidazoles



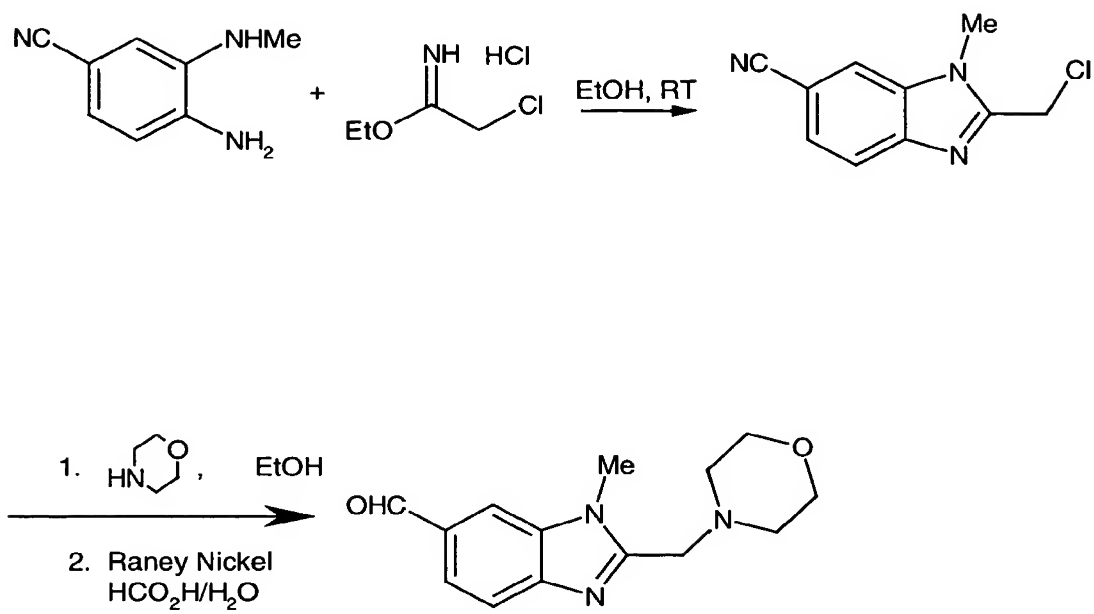
Scheme 3. 1-Aminoethylbenzimidazoles



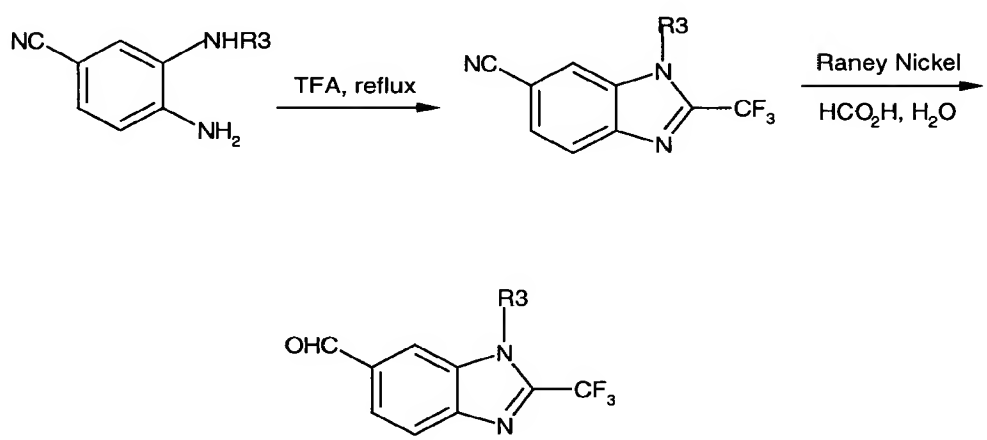
Scheme 4. 2-(Aminoethyl)aminobenzimidazoles



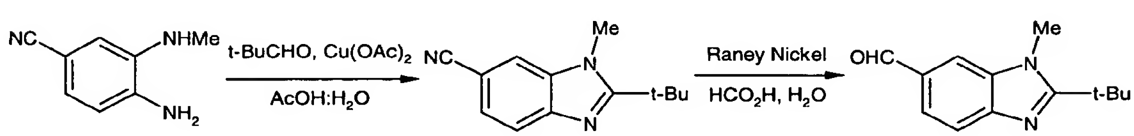
Scheme 5. 2-(Methylamino)benzimidazoles



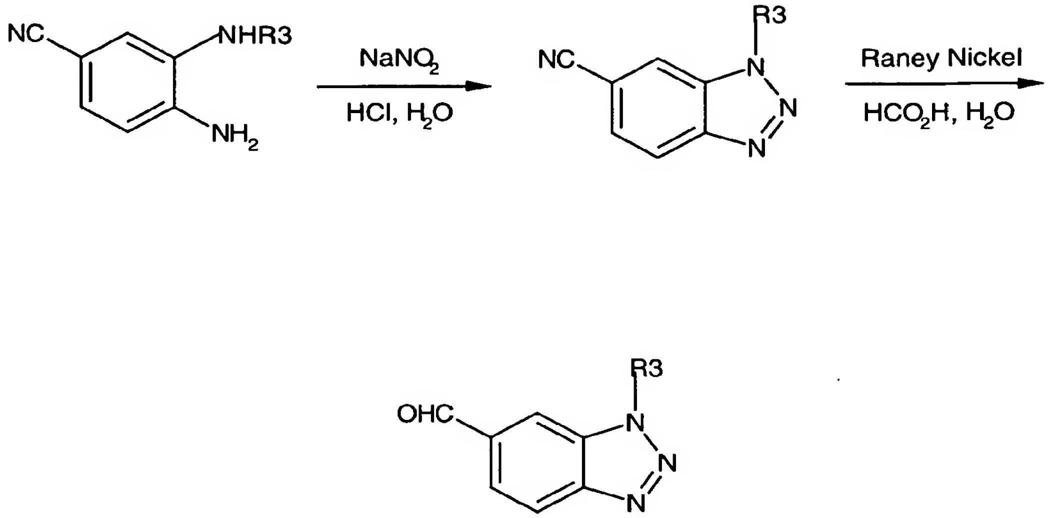
Scheme 6. 2-Trifluoromethylbenzimidazoles



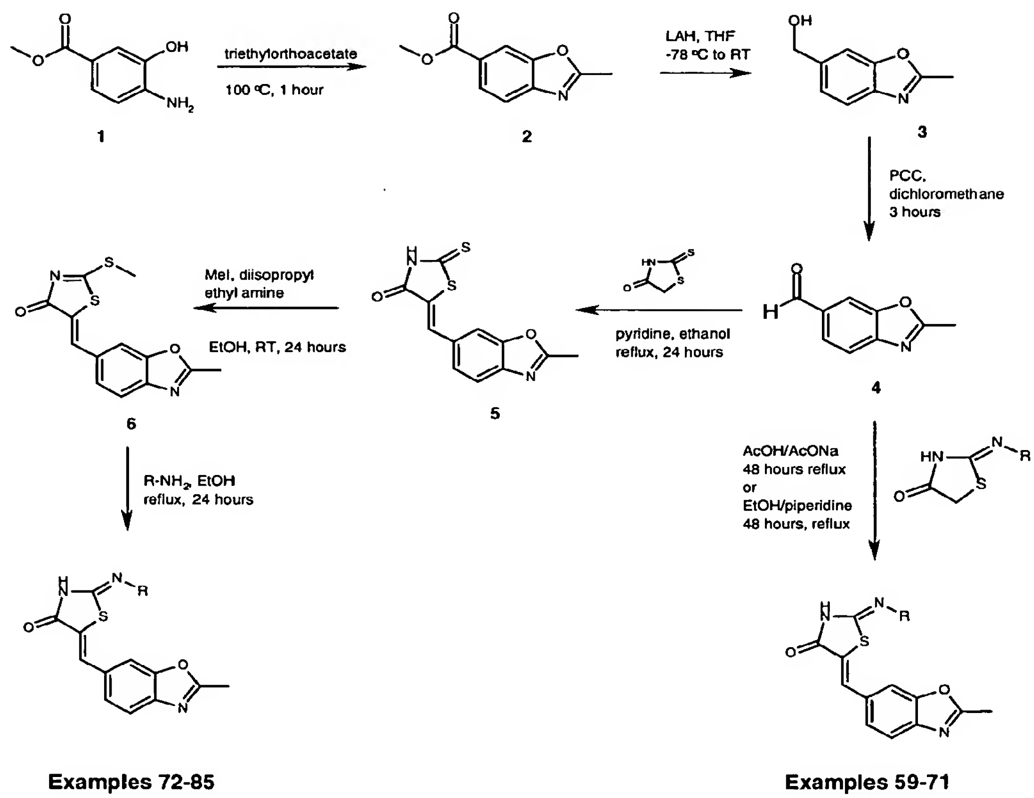
Scheme 7. 2-*t*-Butylbenzimidazoles



Scheme 8. 3-Alkylbenzotriazoles

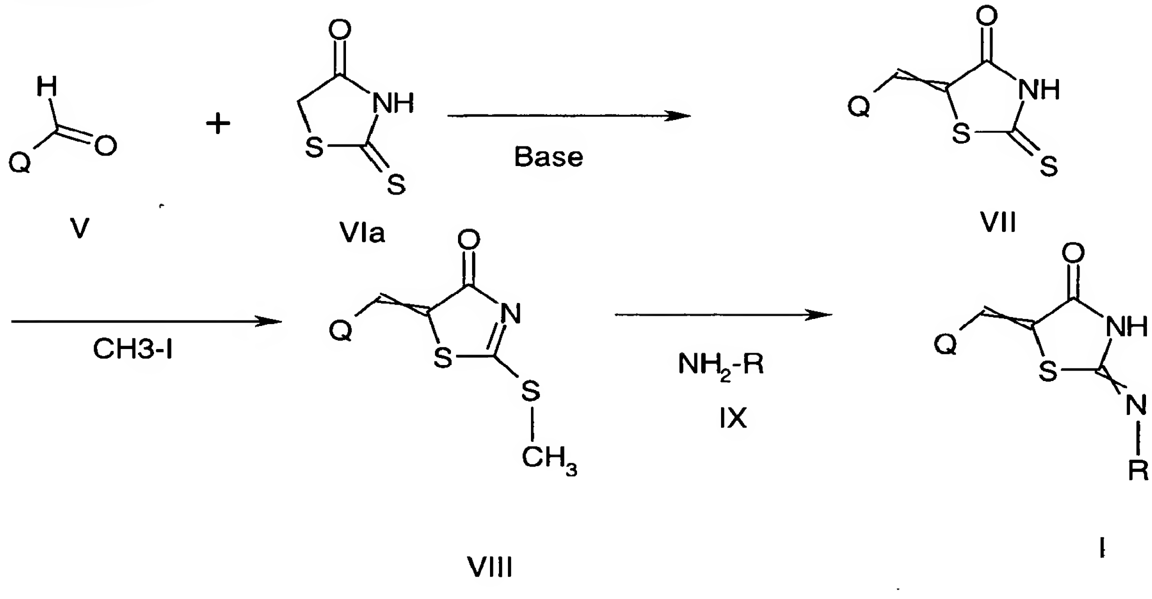

NC
NHR3
NH2
NaNO2
HCl, H2O
R3
Raney Nickel
HCO2H, H2O
OHC

Scheme 9


triethylorthoacetate
100 °C, 1 hour
LAH, THF
-78 °C to RT
PCC,
dichloromethane
3 hours
pyridine, ethanol
reflux, 24 hours
MeI, diisopropyl
ethyl amine
EtOH, RT, 24 hours
R-NH2, EtOH
reflux, 24 hours
AcOH/AcONa
48 hours reflux
or
EtOH/piperidine
48 hours, reflux
1
2
3
4
5
6
Examples 72-85
Examples 59-71

Briefly in Scheme 9, preparation of aldehyde **4** starts with cyclization of methyl 4-amino-3-hydroxy-benzoate **1**. Benzoxazole **2** is formed by the reaction with triethylortho acetate. Other reagents, such us, but not limited to, acetamide, acetic anhydride, acetyl chloride, could be utilized in this reaction. Formed benzoxazole is then isolated from the reaction mixture by filtration. Reduction of the ester to the alcohol **3** is done using lithium aluminum hydride. Other reducing agents, such us, but limited to, DIBAL-H, diborane, sodium-ammonia, sodium borohydride can be used for this reaction. Oxidation of alcohol in the presence of PCC yields aldehyde **4**. Other oxidative reagents, such us MnO_2 or Swern oxidation can be utilized in this case. Coupling of the aldehyde with thiazolidinone utilizing Knoevenagel reaction can proceed under acid or basis catalysis. When benzoxazole undergoes acid-catalyzed reaction, partial formation of the ring-opening product may be observed. Product is then purified by column chromatography. Coupling with rhodanine under basic conditions yields thiazolidinone **5**, which was then methylated with MeI to give thiazolidinone **6**. Other methylating agents suitable for this reaction are diazomethane, methyl sulfoxide or other suitable methylating agents. Displacement with a variety of alkyl and aryl amines is done in ethanol and pure product can be isolated by filtration.

Scheme B



Scheme B is a variant of process of Scheme 9. Briefly in Scheme B, a mixture of an aldehyde of formula V (1 equivalent), rhodanine (1 equivalent), sodium acetate (about 3 equivalents), and acetic acid is heated at around 110 C° for about 48 h. The reaction mixture is cooled to room temperature to afford a product of formula VII.

Then, to a room temperature suspension of VII (1 equivalent) in a suitable solvent such as ethanol is added Hunig's base (about 2 equivalents) followed by iodomethane (about 5 equivalents). Stirring the resultant suspension at room temperature for 3.5 h will yield a compound of VIII. To a mixture of VIII (1 equivalent) and MS4A powder is added an amine of formula IX (1~2 equivalent) and ethanol (dehydrated). The mixture was heated to afford a compound of formula I.

In the above Schemes, the meaning of R, R1, R3, and Q are as defined for formula I.

Specific Embodiments - Examples

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
μL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
i. v. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	rt (room temperature);
min (minutes);	h (hours);
mp (melting point);	TLC (thin layer chromatography);
Tr (retention time);	RP (reverse phase);
MeOH (methanol);	i-PrOH (isopropanol);
TEA (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);

DMSO (dimethylsulfoxide); AcOEt (ethyl acetate);
DME (1,2-dimethoxyethane); DCM (dichloromethane);
DCE (dichloroethane); DMF (N,N-dimethylformamide);
DMPU (N,N'-dimethylpropyleneurea); (CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate); HOAc (acetic acid);
HOSu (N-hydroxysuccinimide); HOBT (1-hydroxybenzotriazole);
mCPBA (meta-chloroperbenzoic acid; EDC (ethylcarbodiimide hydrochloride);
BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);

Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); BSA (bovine serum albumin)
ATP (adenosine triphosphate); HRP (horseradish peroxidase);
DMEM (Dulbecco's modified Eagle medium);
HPLC (high pressure liquid chromatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
TBAF (tetra-n-butylammonium fluoride);
HBTU (O-Benzotriazole-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate).
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
DPPA (diphenylphosphoryl azide);
fHNO3 (fumed HNO3); and
EDTA (ethylenediaminetetraacetic acid).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

^{1}H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, a Brucker AVANCE-400, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz

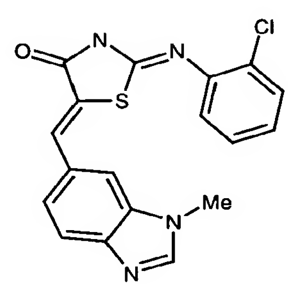
(Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102, or a SCIEX-APIiii spectrometer; LC-MS were recorded on a micromass 2MD and Waters 2690; high resolution MS were obtained using a JOEL SX-102A spectrometer. All mass spectra were taken under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI) or by fast atom bombardment (FAB) methods. Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

In the present specification, often the regiochemistry around the double bonds in the chemical formulas are drawn as fixed for ease of representation; however, a skilled in the art will readily appreciate that the compounds will naturally assume more thermodynamically stable structure around the C=N (the imine) double bond, if they exit, as exo form. Further compounds can also exit in endo form. As stated before, the invention contemplates both endo and exo forms as well as both regioisomers around the exo imine bond. Further it is intended that both E and Z isomers are encompassed around the C=C double bond.

Example 1

(5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one



(a) 3-(Methyloxy)-4-nitrobenzonitrile. Following the procedure of Mackman *et al.* in *J. Med. Chem.* **2001**, *44*, 2753-2771, 3-methoxy-4-nitrobenzoic acid (11.52 g, 58.4 mmol) was dissolved in THF (158 mL) and cooled to 0 □C. Oxalyl chloride (5.6 mL, 64.3 mmol) was added dropwise under a nitrogen atmosphere, followed by a few drops of DMF. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then concentrated to dryness under reduced pressure, and the residue redissolved in THF (158 mL) and cooled to 0 □C. Ammonia gas was bubbled through the solution for 10 min, leading to the formation of a yellow precipitate. The ice bath was removed, and the mixture was sealed and allowed to stir overnight. After the addition of EtOAc (100 mL), the solids were filtered off, washed with water, and dried to provide 3-(methyloxy)-4-nitrobenzamide (10.10 g, 88%) as a yellow solid. Additional product could be recovered from the filtrate by removal of the organic solvent under reduced pressure, then redissolving the residue in EtOAc. The organic layer was washed with 1N HCl (2 x 100 mL), brine (2 x 100 mL), then dried (Na_2SO_4), filtered and concentrated to afford an additional 1.07 g (9%). ^1H NMR (d_6-DMSO): □ 8.25 (bs, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.73 (s, 1H), 7.57 (dd, J = 1.6, 8.4 Hz, 1H), 3.98 (s, 3H).

To a suspension of 3-(methyloxy)-4-nitrobenzamide (11.17 g, 56.7 mmol) in THF (150 mL) was added Et_3N (10.3 mL, 73.7 mmol), followed by the dropwise addition of TFAA (8.67 mL, 62.4 mmol). After stirring for 1.5 h, the solvent was removed *in vacuo* and the mixture dissolved in EtOAc (400 mL). The solution was washed with 1N HCl (1 x 200 mL), brine (2 x 250 mL), dried over Na_2SO_4, filtered and concentrated to yield 3-(methyloxy)-4-nitrobenzonitrile (9.98 g, 96% overall) as a yellow solid. ^1H NMR (d_6-DMSO): □ 8.06 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.64 (dd, J = 1.2, 8.4 Hz, 1H), 3.98 (s, 3H).

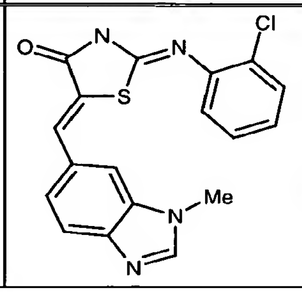
(b) 3-(Methylamino)-4-nitrobenzonitrile. Following the procedure of Mackman *et al.* in *J. Med. Chem.* **2001**, *44*, 2753-2771, 3-methoxy-4-nitrobenzonitrile (1.0 g, 5.62 mmol) was dissolved in DMSO (7 mL) in a pressure tube and a 40% solution of $MeNH_2$ in water (1 mL) was added. The tube was sealed and heated to 75 □C for 4 h, then cooled and poured onto an ice/water mixture. The precipitate was filtered, rinsed with water, and dried to afford 3-(methylamino)-4-nitrobenzonitrile (0.95 g, 95%) as an orange solid. ^1H NMR ($CDCl_3$): □8.26 (d, J = 8.8 Hz, 1H), 8.05 (bs, 1H), 7.15 (d, J = 1.2 Hz, 1H), 6.89 (dd, J = 1.6, 8.8 Hz, 1H), 3.06 (d, J = 5.2 Hz, 3H).

(c) 4-Amino-3-(methylamino)benzonitrile. To a mixture of 3-(methylamino)-4-nitrobenzonitrile (0.655 g, 3.70 mmol) in MeOH (9.5 mL) and EtOAc (9.5 mL) was added 10% Pd/C (65 mg). After stirring under a hydrogen atmosphere for 4 h, the reaction mixture was filtered through a pad of Celite, rinsed with MeOH, and concentrated under reduced pressure to afford 4-amino-3-(methylamino)benzonitrile (0.542 g, 100%) as a beige solid. ^1H NMR ($CDCl_3$): □7.02 (dd, J = 1.6, 8.0 Hz, 1H), 6.84 (d, J = 1.2 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.74 (bs, 2H), 3.32 (bs, 1H), 2.87 (s, 3H).

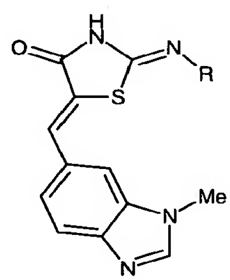
(d) 1-Methyl-1*H*-benzimidazole-6-carbaldehyde. A mixture of 4-amino-3-(methylamino)benzonitrile (0.40 g, 2.72 mmol) in HCO_2H (9 mL) was heated to 100 □C for 2 h. The mixture of crude benzimidazole was then cooled, Raney nickel (0.4 g) and H_2O (2 mL) were added, and the mixture was heated again to 100 □C for 1 h. The hot mixture was then filtered through Celite, rinsed with MeOH and concentrated under reduced pressure. Water (1 mL) was added to the residue, which was then treated carefully with sat. aq. $NaHCO_3$. The solid which precipitated was filtered, rinsed with H_2O and dried to afford 1-methyl-1*H*-benzimidazole-6-carbaldehyde (0.412 g, 95%) as a tan solid, which was used

directly in the next reaction. ^{1}H NMR ($CDCl_3$): □10.12 (s, 1H), 8.05 (s, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 1.2, 8.0 Hz, 1H), 3.94 (s, 3H).

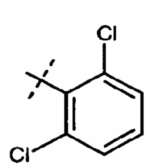
(e) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one. A solution of 1-methyl-1*H*-benzimidazole-6-carbaldehyde (15 mg, 0.094 mmol), 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one (21.3 mg, 0.094 mmol), and piperidine (18.5 □L, 0.188 mmol) in EtOH (0.5 mL) was heated in a microwave reactor at 170 □C for 720 s. The solvent was then removed under reduced pressure and the crude product purified by precipitation from a mixture of CH_2Cl_2/hexanes. Alternatively, the product could be purified by column chromatography.

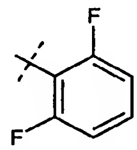
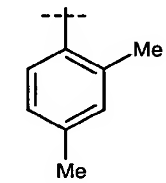
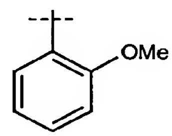
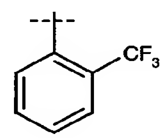
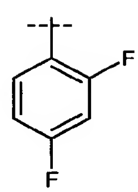
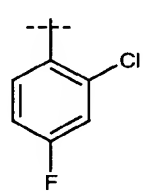
Example	Compound name	Structure	NMR (400 MHz)
1	(5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.95 (s, 1H), 7.92 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.48 (m, 2H), 7.39 (dd, J = 0.8, 8.8 Hz, 1H), 7.31 (dt, J = 1.6, 7.6 Hz, 1H), 7.17 (dt, J = 1.6, 7.6 Hz, 1H), 7.08 (m, 1H), 3.86 (s, 3H)

Examples 2-8



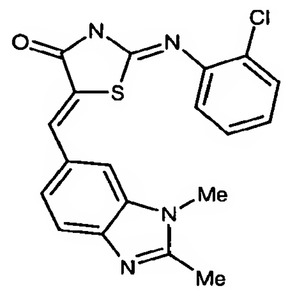
The following compounds were prepared according to the procedure of Example 1, except substituting the appropriately substituted thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R	NMR (400 MHz)
2	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(d_6-acetone): 8.11 (s, 1H), 7.70 (m, 3H), 7.43 (m, 3H), 7.12 (m, 1H), 3.91 (s, 3H)

3	(5*Z*)-2-[(2,6-difluorophenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.95 (s, 1H), 7.92 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.38 (m, 1H), 7.12 (m, 1H), 7.00 (t, *J* = 7.6 Hz, 2H), 3.89 (s, 3H)
4	(5*Z*)-2-[(2,4-dimethylphenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.93 (s, 1H), 7.90 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.39 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.10 (s, 1H), 7.05 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H)
5	(5*Z*)-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-2-{[2-(methyloxy)phenyl]amino}-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.95 (s, 1H), 7.84 (m, 1H), 7.51 (m, 2H), 6.99 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H)
6	(5*Z*)-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-2-{[2-(trifluoromethyl)phenyl]amino}-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.94 (s,1H); 7.89 (s, 1H), 7.80 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.56 (m, 2H), 7.45 (m, 1H), 7.38 (m, 1H), 7.10 (m, 1H), 3.85 (s, 3H)
7	(5*Z*)-2-[(2,4-difluorophenyl)amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		($CDCl_3$): 7.95 (s, 1H), 7.88 (m, 1H), 7.43 (m, 1H), 7.35 (m, 2H), 6.92 (m, 2H), 3.74 (s, 3H), 2.63 (s, 3H)
8	(5*Z*)-2-[(2-chloro-4-fluorophenyl)-amino]-5-[(1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 9.33 (s, 1H), 8.01 (s, 1H), 7.88 (m, 2H), 7.74 (dd, J = 1.6, 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 6.4 Hz, 2H), 4.11 (s, 3H)

Example 9

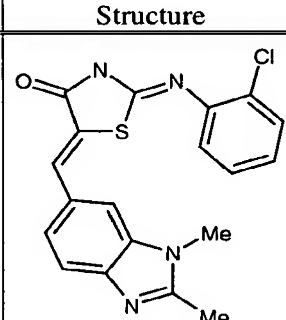
(5Z)-2-[(2-Chlorophenyl)amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one



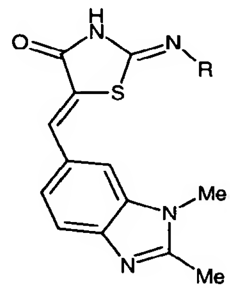
(a) 1,2-Dimethyl-1*H*-benzimidazole-6-carbonitrile. 4-Amino-3-(methylamino)benzonitrile (from Example 1(c); 0.500 g, 3.40 mmol) and 2,4-pentanedione (0.700 mL, 6.80 mmol) were dissolved in EtOH (8.4 mL) and cooled to 0 □C. 6N HCl (2.8 mL) was added dropwise and the solution turned deep red. Stirring was continued for 20 min, after which time the mixture was carefully poured onto ice/sat. aq. $NaHCO_3$, making sure the aqueous layer remained basic. The solid product which precipitated was filtered off, rinsed with H_2O and dried to afford the crude 1,2-dimethyl-1*H*-benzimidazole-6-carbonitrile (0.355 g, 61%). ^1H NMR ($CDCl_3$): □7.72 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, 1H), 7.50 (dd, *J* = 1.2, 8.4 Hz, 1H), 3.78 (s, 3H), 2.66 (s, 3H).

(b) 1,2-Dimethyl-1H-benzimidazole-6-carbaldehyde. A mixture of 1,2-dimethyl-1*H*-benzimidazole-6-carbonitrile (0.355 g, 2.08 mmol) and Raney nickel (150 mg) was suspended in HCO_2H (7 mL) and H_2O (3 mL) and heated to 100 □C for 2 h. The mixture was then filtered hot through Celite, rinsed with MeOH, and concentrated. To the resulting residue was added H_2O (1 mL) followed by sat. aq. $NaHCO_3$ until basic. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL), dried over Na_2SO_4, and concentrated to yield the product aldehyde (0.284 g, 79%) as a beige solid. ^1H NMR ($CDCl_3$): □10.07 (s, 1H), 7.88 (t, J = 1.2 H, 1H), 7.77 (d, J = 1.2 Hz, 2H), 3.81 (s, 3H), 2.61 (s, 3H).

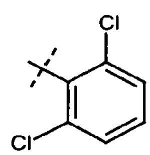
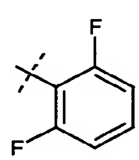
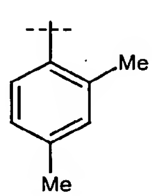
(c) (5Z)-2-[(2-Chlorophenyl)amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

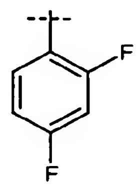
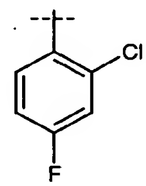
Example	Compound name	Structure	NMR (400 MHz)
9	(5Z)-2-[(2-Chlorophenyl)-amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)-methylidene]-1,3-thiazol-4(5*H*)-one		(d_6-DMSO): 12.58 (s, 1H),.7.81 (s, 1H), 7.72 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (m, 1H), 7.23 (m, 3H), 3.72 (s, 3H), 2.53 (s, 3H)

Examples 10-14



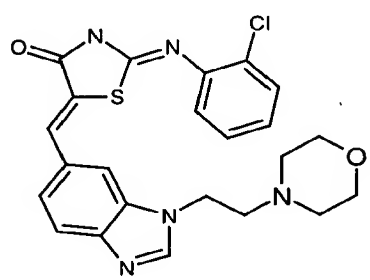
The following compounds were prepared according to the procedure of Example 9, except substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R	NMR (400 MHz)
10	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(d_6-DMSO): 7.57 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.41 (m, 2H), 7.26 (m, 1H), 6.97 (m, 1H), 3.29 (s, 3H), 2.5 (s, 3H)
11	(5*Z*)-2-[(2,6-difluorophenyl)amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.85 (s, 1H), 7.56 (m, 2H), 7.33 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.20 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 2H), 3.76 (s, 3H), 2.59 (s, 3H)
12	(5*Z*)-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-2-[(2,4-dimethylphenyl)amino]-1,3-thiazol-4(5*H*)-one		(d_6-DMSO): 7.76 (d, *J* = 3.6 Hz, 1H), 7.71 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.10 (s, 1H), 7.02 (m, 1H), 3.71 (s, 3H), 3.29 (s, 3H), 2.53 (s, 3H), 2.29 (s, 3H)

13	(5Z)-2-[(2,4-difluorophenyl) amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.83 (s, 1H), 7.58 (m, 2H), 7.36 (m, 1H), 7.06 (m, 3H), 3.77 (s, 3H), 2.60 (s, 3H)
14	(5Z)-2-[(2-chloro-4-fluorophenyl) amino]-5-[(1,2-dimethyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.82 (s, 1H), 7.57 (m, 2H), 7.35 (dd, J = 0.8, 8.8 Hz, 1H), 7.31 (d, J = 8.8 hz, 1H), 7.12 (d, J = 5.6 Hz, 2H), 3.77 (s, 3H), 2.60 (s, 3H)

Example 15

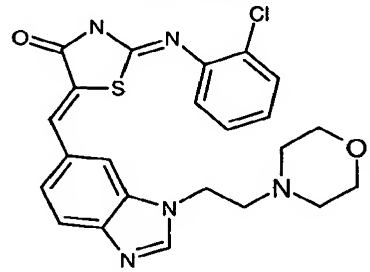
(5Z)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one



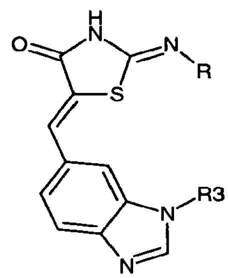
(a) 4-Amino-3-{[2-(4-morpholinyl)ethyl]amino}benzonitrile. A mixture of 3-methoxy-4-nitrobenzonitrile (from Example 1(a); 0.178g, 1.0 mmol) and 4-(2-aminoethyl)morpholine (0.65 mL, 5.0 mmol) were heated to 80 □C for 20 h. The reaction mixture was cooled, diluted with EtOAc (50 mL), and washed with H_2O (3 x 30 mL) and brine (1 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford 3-{[2-(4-morpholinyl)ethyl]amino}-4-nitrobenzonitrile (0.246 g, 89%) as a red solid. This material was dissolved in MeOH (3 mL), 10% Pd/C (24 mg) was added, and the mixture stirred under a hydrogen atmosphere overnight. Filtration through Celite and removal of the solvent provided the desired diaminobenzonitrile (0.219 g, 100%) as a red oil.

(b) 1-[2-(4-Morpholinyl)ethyl]-1*H*-benzimidazole-6-carbaldehyde. According to the procedure in Example 1(d), 4-amino-3-{[2-(4-morpholinyl)ethyl]amino}benzonitrile was converted to the benzimidazole carboxaldehyde in 72% yield. ^1H NMR ($CDCl_3$): □10.11 (s, 1H), 8.20 (s, 1H), 8.02 (d, J = 0.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 1.2, 8.4 Hz, 1H), 4.34 (t, J = 6.0 Hz, 2H), 3.69 (t, J = 4.4 Hz, 4H), 2.98 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 4.8 Hz, 4H).

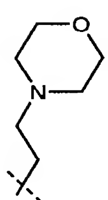
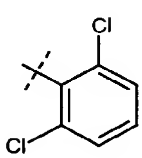
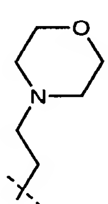
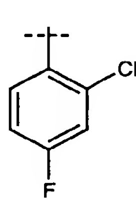
(c) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

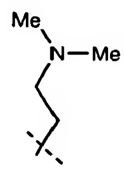
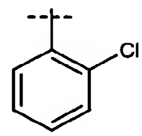
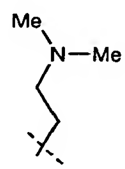
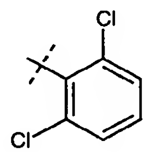
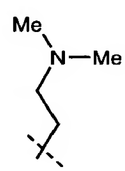
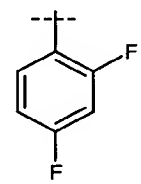
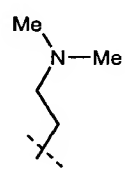
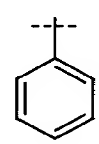
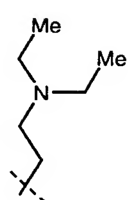
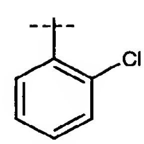
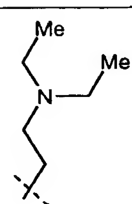
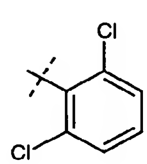
Example	Compound name	Structure	NMR (400 MHz)
15	(5*Z*)-2-[(2-Chlorophenyl)-amino]-5-({1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-6-yl}-methylidene)-1,3-thiazol-4(5*H*)-one		(CD_3OD): 8.30 (s, 1H), 7.84 (s, 1H), 7.72 (m, 2H), 7.48 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.41 (m, 1H), 7.33 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.19 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.09 (m, 1H), 4.39 (t, *J* = 6.4 Hz, 2H), 3.59 (m, 4H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.43 (m, 4H)

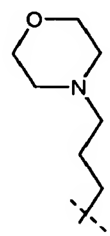
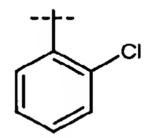
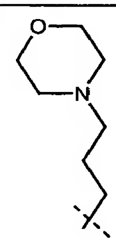
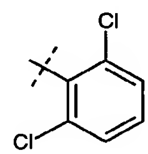
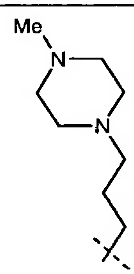
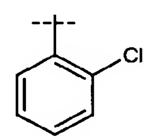
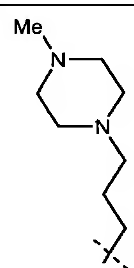
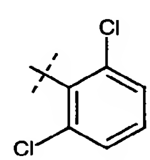
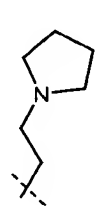
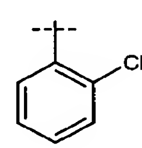
Examples 16-32

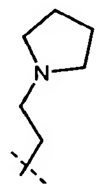
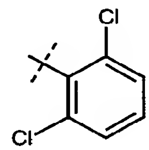
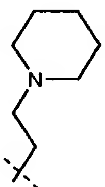
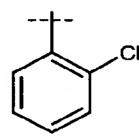
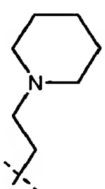
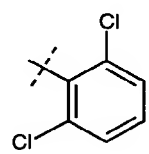
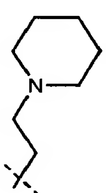
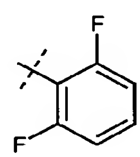


The following compounds were prepared according to the procedure of Example 15, using the requisite amine for 4-(2-aminoethyl)morpholine and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R3	R	NMR (400 MHz)
16	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[2-(4-morpholinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.30 (s, 1H), 7.87 (s, 1H), 7.72 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.15 (m, 1H), 4.39 (t, *J* = 5.6 Hz, 2H), 3.60 (m, 4H), 2.74 (t, *J* =5.6 Hz, 2H), 2.44 (m, 4H)
17	(5*Z*)-2-[(2-chloro-4-fluorophenyl) amino]-5-({1-[2-(4-morpholinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.30 (s, 1H), 7.85 (s, 1H), 7.72 (m, 2H), 7.41 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.33 (dd, *J* = 1.2, 9.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 4.40 (t, *J* = 6.4 Hz, 2H), 3.59 (m, 4H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.44 (m, 4H)

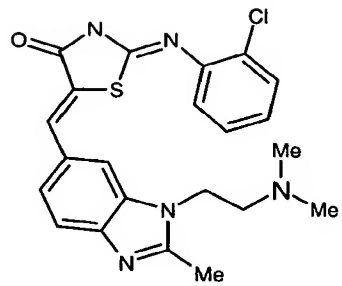
18	(5*Z*)-2-[(2-chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.28 (s, 1H), 7.84 (s, 1H), 7.74 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.37 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H)
19	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.24 (s, 1H), 7.71 (m, 3H), 7.40 (m, 3H), 7.10 (t, *J* = 8.0 Hz, 1H), 4.35 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.19 (s, 6H).
20	(5*Z*)-2-[(2,4-difluorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.30 (s, 1H), 7.84 (s, 1H), 7.74 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.10 (m, 2H), 6.98 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.23 (s, 6H)
21	(5*Z*)-5-({1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-2-(phenylamino)-1,3-thiazol-4(5*H*)-one			(CD_3OD, mixture of two isomers): 8.35 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.70-7.88 (m, 8H), 7.57 (m, 1H), 7.41 (m, 5H), 7.23 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 4.48 (m, 2H), 4.38 (m, 2H), 2.86 (m, 2H), 2.74 (m, 2H), 2.35 (s, 6H), 2.22 (s, 6H)
22	(5*Z*)-2-[(2-chlorophenyl)amino]-5-({1-[2-(diethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.27 (s, 1H), 7.84 (s, 1H), 7.71 (m, 2H), 7.48 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (dd, *J* = 0.8, 8.0 Hz, 1H), 4.32 (t, *J* = 6.0 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.48 (q, *J* = 7.2 Hz, 4H), 0.86 (t, *J* = 7.2 Hz, 6H)
23	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(diethylamino)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-			(CD_3OD): 8.27 (s, 1H), 7.85 (s, 1H), 7.70 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.47 (q, *J* = 6.8 Hz, 4H), 0.86 (t, *J* = 6.8 Hz, 6H)

	one			
24	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({1-[3-(4-morpholinyl) propyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.29 (s, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 4.36 (t, J = 6.8 Hz, 2H), 3.60 (bs, 4H), 2.32 (bs, 4H), 2.26 (t, J = 6.8 Hz, 2H), 2.04 (t, J = 6.8 Hz, 2H)
25	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[3-(4-morpholinyl) propyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 9.09 (m, 1H), 8.01 (bs, 1H), 7.91 (s, 1H), 7.85 (m, 1H), 7.61 (m, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 4.58 (bs, 2H), 4.02 (m, 2H), 3.75 (m, 2H), 3.47 (m, 2H), 3.25 (bs, 2H), 3.12 (m, 2H), 2.42 (bs, 2H)
26	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({1-[3-(4-methyl-1-piperazinyl) propyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.27 (s, 1H), 7.81 (s, 1H), 7.74 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 4.34 (t, J = 6.4 Hz, 2H), 2.46 (bs, 8H), 2.30 (s, 3H), 2.27 (t, J = 6.4 Hz, 2H), 2.03 (t, J = 6.4 Hz, 2H)
27	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[3-(4-methyl-1-piperazinyl) propyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 9.37 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 4.59 (m, 2H), 2.89 (s, 3H), 2.83 (m, 8H), 2.62 (bs, 2H), 2.22 (t, J = 6.4 Hz, 2H)
28	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-			(CD_3OD): 8.29 (s, 1H), 7.84 (s, 1H), 7.71 (m, 2H), 7.47 (dd, J = 0.8, 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.32 (dt, J = 0.8, 7.6 Hz, 1H), 7.18 (dt, J = 0.8, 7.6 Hz, 1H), 7.09 (dd, J = 1.6, 8.0 Hz, 1H), 4.40 (t, J = 6.4 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H),

	1,3-thiazol-4(5*H*)-one			2.53 (bs, 4H), 1.76 (bs, 4H)
29	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[2-(1-pyrrolidinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.30 (s, 1H), 7.87 (s, 1H), 7.72 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 0.4, 9.2 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.43 (t, *J* = 6.4 Hz, 2H), 2.96 (m, 2H), 2.56 (bs, 4H), 1.78 (bs, 4H)
30	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({1-[2-(1-piperidinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.29 (s, 1H), 7.89 (s, 1H), 7.85 (m, 2H), 7.47 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* =8.0 Hz, 1H), 4.40 (2H, 6.4 Hz, 2H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.44 (bs, 4H), 1.54 (m, 6H)
31	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[2-(1-piperidinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.29 (s, 1H), 7.86 (s, 1H), 7.71 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.40 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.44 (bs, 4H), 1.54 (m, 6H)
32	(5*Z*)-2-[(2,6-difluorophenyl) amino]-5-({1-[2-(1-piperidinyl) ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.32 (s, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.21 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 2H), 4.50 (t, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.60 (bs, 4H), 1.62 (m, 4H), 1.49 (m, 2H)

Example 33

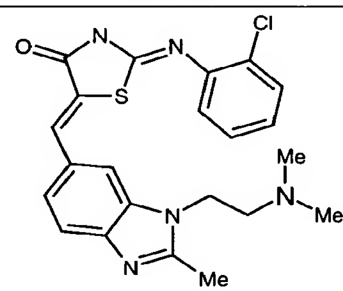
(5*Z*)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one



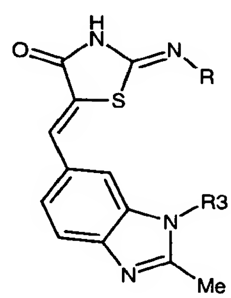
(a) 4-Amino-3-{[2-(dimethylamino)ethyl]amino}benzonitrile. Following the procedure outlined in Example 15(a), 3-methoxy-4-nitrobenzonitrile was converted into 4-amino-3-{[2-(dimethylamino)ethyl]amino}benzonitrile in quantitative yield using N,N-dimethylethylenediamine as the nucleophile. ^{1}H NMR ($CDCl_3$): □7.01 (dd, J = 1.6, 8.0 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 3.98 (m, 2H), 3.12 (m, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.26 (s, 3H).

(b) 1-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-benzimidazole-6-carbaldehyde. The title compound was synthesized according to the procedure in Example 9(a) and 9(b), starting from 4-amino-3-{[2-(dimethylamino)ethyl]amino}benzonitrile. ^{1}H NMR ($CDCl_3$): □10.07 (s, 1H), 7.88 (d, J = 1.2 Hz, 1H), 7.77 (s, 2H0, 4.25 (m, 2H), 2.68 (s, 3H), 2.67 (m, 2H), 2.31 (s, 6H).

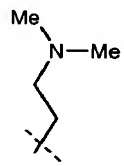
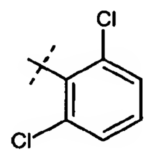
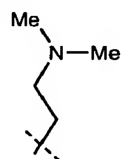
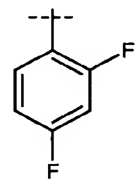
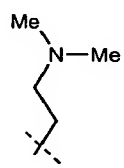
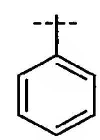
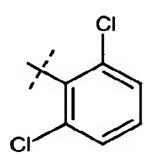
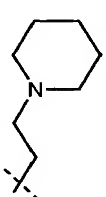
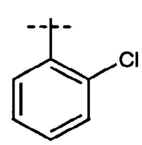
(c) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

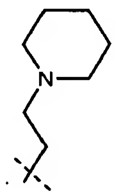
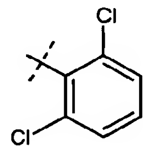
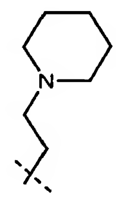
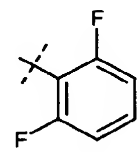
Example	Compound name	Structure	NMR (400 MHz)
33	(5*Z*)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.81 (s, 1H), 7.60 (m, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.28 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.61 (s, 3H), 2.21 (s, 6H)

Examples 34-40

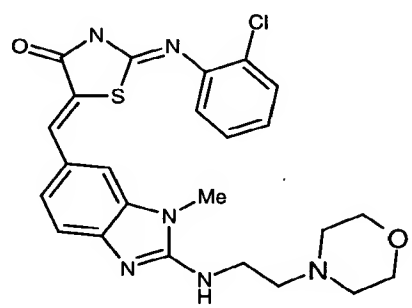


The following compounds were prepared according to the procedure of Example 33, using the requisite amine for N,N-dimethylethylenediamine and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R3	R	NMR (400 MHz)
34	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[2-(dimethylamino) ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.84 (s, 1H), 7.58 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.62 (s, 3H), 2.21 (s, 6H)
35	(5*Z*)-2-[(2,4-difluorophenyl) amino]-5-({1-[2-(dimethylamino) ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.84 (s, 1H), 7.61 (m, 2H), 7.38 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.99-7.14 (m, 3H), 4.34 (t, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.63 (s, 3H), 2.31 (s, 6H)
36	(5*Z*)-5-({1-[2-(dimethylamino) ethyl]-2-methyl-1*H*-benzimidazol-6-yl}methylidene)-2-(phenylamino)-1,3-thiazol-4(5*H*)-one			(CD_3OD, mixture of two isomers): 7.09-7.95 (m, 9H), 4.28-4.39 (m, 2H), 2.61-2.76 (m, 5H), 2.37 (s, 3H), 2.23 (s, 3H)
37	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-{[1-(2-hydroxyethyl)-2-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.85 (s, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 4.4 Hz, 2H), 3.85 (t, *J* = 4.4 Hz, 2H), 2.64 (s, 3H)
38	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.83 (s, 1H), 7.60 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.63 (s, 3H), 2.43 (bs, 4H), 1.54 (m, 4H), 1.46 (m, 2H)

39	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.85 (s, 1H), 7.68 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.63 (s, 3H), 2.44 (bs, 4H), 1.54 (m, 4H), 1.46 (m, 2H)
40	(5*Z*)-2-[(2,6-difluorophenyl)amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.85 (s, 1H), 7.59 (m, 2H), 7.35 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.19 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 2H), 4.33 (t, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.63 (s, 3H), 2.47 (bs, 1H), 1.55 (m, 4H), 1.47 (m, 2H)

Example 41
(5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one



(a) 3-Methyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carbonitrile. A suspension of 4-amino-3-(methylamino)benzonitrile (0.500 g, 3.40 mmol) and 1,1'-carbonyldiimidazole (1.10 g, 6.80 mmol) in THF (8.5 mL) was stirred at room temperature for 2 days. The reaction mixture was filtered, the collected solid rinsed with small amounts of H_2O and EtOAc, and dried to afford the cyclic urea (0.489 g, 83%) as a pink solid. Additional material could be recovered from the filtrate by separating the organic layer, washing with 0.1N HCl (1 x 30 mL), brine (1 x 30 mL), and drying over Na_2SO_4. After filtration, removal of solvent yielded 40 mg (7%) of additional product. ^1H NMR (d_6-acetone): □10.23 (bs, 1H), 7.46 (s, 1H), 7.42 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 3.40 (s, 3H).

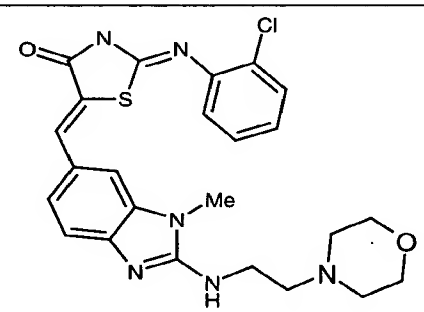
(b) 2-Chloro-1-methyl-1*H*-benzimidazole-6-carbonitrile. A mixture of 3-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carbonitrile (0.219 g, 1.26 mmol) in $POCl_3$ (2.5 mL) was heated to 105 □C overnight. Upon cooling, the excess $POCl_3$ was removed under reduced vacuum, the residue diluted with H_2O and CH_2Cl_2, and the solution made basic with 1N NaOH. The layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and

concentrated to afford the 2-chlorobenzimidazole (0.191 g, 80%) as a tan solid. ^{1}H NMR ($CDCl_3$): □7.76 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.65 (dd, *J* = 0.8, 1.6 Hz, 1H), 7.55 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.85 (s, 3H).

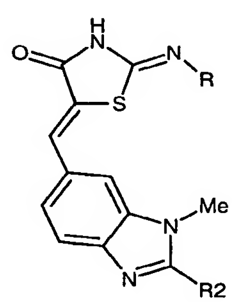
(c) 1-Methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1*H*-benzimidazole-6-carbonitrile. A solution of 2-chloro-1-methyl-1*H*-benzimidazole-6-carbonitrile (50 mg, 0.262 mmol) and 4-(2-aminoethyl)morpholine (136 mg, 1.05 mmol) in EtOH (1.3 mL) was heated in a sealed vial to 80 □C for 24 h. The cooled reaction mixture was concentrated and the crude residue purified by column chromatography to yield the 2-aminobenzimidazole (66 mg, 88%). ^{1}H NMR ($CDCl_3$): □7.45 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.32 (d, *J* = 0.8 Hz, 1H), 5.25 (m, 1H), 3.74 (t, *J* = 4.8 Hz, 4H), 3.64 (m, 2H), 3.53 (s, 3H), 2.70 (t, *J* = 5.6 Hz, 2H), 2.53 (t, *J* = 4.4 Hz, 4H).

(d) 1-Methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1*H*-benzimidazole-6-carbaldehyde. Following the procedure of Example 9(b), the benzimidazole-6-carbonitrile from Example 41(c) was reduced to the aldehyde in 73% yield. ^{1}H NMR ($CDCl_3$): □9.56 (s, 1H), 7.63 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 5.27 (bs, 1H), 3.74 (t, *J* = 4.8 Hz, 4H), 3.66 (app. quartet, *J* = 4.8, 11.2 Hz, 2H), 3.56 (s, 3H), 2.71 (t, *J* = 5.6 Hz, 2H), 2.54 (t, *J* = 4.4 Hz, 4H).

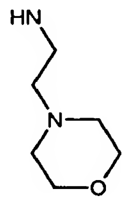
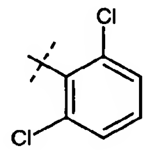
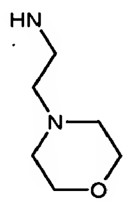
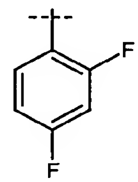
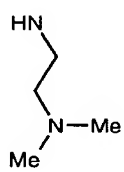
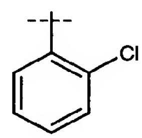
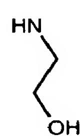
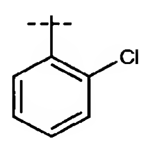
(e) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

Example	Compound name	Structure	NMR (400 MHz)
41	(5*Z*)-2-[(2-Chloro-phenyl)-amino]-5-[(1-methyl-2-{[2-(4-morpholinyl) ethyl]-amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(d_6-acetone): 7.76 (s, 1H), 7.51 (m, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.30 (m, 2H), 7.21 (m, 2H), 7.16 (m, 1H), 3.60 (m, 10H), 2.64 (m, 2H), 2.49 (bs, 4H)

Examples 42-45

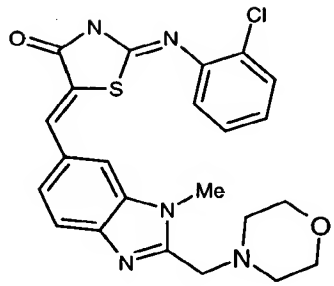


The following compounds were prepared according to the procedure of Example 41, using the requisite amine for 4-(2-aminoethyl)morpholine and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R2	R	NMR (400 MHz)
42	(5Z)-2-[(2,6-dichlorophenyl) amino]-5-[(1-methyl-2-{[2-(4-morpholinyl) ethyl]amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.67 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (m, 1H), 7.19 (m, 2H), 7.11 (m, 1H), 3.71 (m, 4H), 3.59 (m, 2H), 3.50 (s, 3H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.68 (m, 2H), 2.55 (m, 4H)
43	(5Z)-2-[(2,4-difluorophenyl) amino]-5-[(1-methyl-2-{[2-(4-morpholinyl) ethyl]amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.74 (s, 1H), 7.37 (m, 1H), 7.29 (m, 1H), 7.22 (m, 1H), 7.06 (m, 3H), 3.70 (bs, 4H), 3.59 (m, 2H), 3.52 (s, 3H), 2.68 (m, 2H), 2.56 (bs, 4H).
44	(5Z)-2-[(2-chlorophenyl) amino]-5-[(2-{[2-(dimethylamino) ethyl]amino}-1-methyl-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.71 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.32 (m, 2H), 7.17 (m, 3H), 7.10 (m, 1H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.51 (s, 3H), 2.73 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 6H)
45	(5Z)-2-[(2-chlorophenyl) amino]-5-({2-[(2-hydroxyethyl) amino]-1-methyl-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.76 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 0.8, 7.2 Hz, 1H), 7.20 (m, 3H), 7.09 (m, 1H), 3.76 (t, *J* = 5.2 Hz, 2H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.51 (s, 3H)

Example 46

(5Z)-2-[(2-Chlorophenyl)amino]-5-{[1-methyl-2-(4-morpholinylmethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one



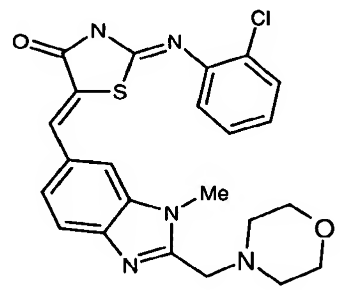
(a) 2-(Chloromethyl)-1-methyl-1*H*-benzimidazole-6-carbonitrile. To a mixture of 4-amino-3-(methylamino)benzonitrile (0.20 g, 1.36 mmol) in EtOH (6.8 mL) was added ethyl 2-chloroethanimidoate hydrochloride (0.43 g, 2.72 mmol; prepared according to Stillings *et al.* in *J. Med. Chem.* **1986**, *29*, 2280-2284). The mixture was stirred overnight and the solvent removed. The residue was diluted with H_2O and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced vacuum to afford the crude benzimidazole (0.266 g, 95%). ^{1}H NMR ($CDCl_3$): □7.82 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.56 (dd, J = 1.2, 8.4 Hz, 1H), 4.86 (s, 2H), 3.93 (s, 3H).

(b) 1-Methyl-2-(4-morpholinylmethyl)-1*H*-benzimidazole-6-carbonitrile. To a mixture of 2-(chloromethyl)-1-methyl-1*H*-benzimidazole-6-carbonitrile (60 mg, 0.293 mmol) in EtOH (1 mL) was added morpholine (0.1 mL, 1.17 mmol). The mixture was heated to reflux for 1 h, cooled and concentrated to dryness. The residue was taken up in CH_2Cl_2 and treated with sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed in vacuo to provide the 2-methylmorpholino benzimidazole (73 mg, 100%). ^{1}H NMR ($CDCl_3$): □7.78 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.52 (dd, J = 1.2, 8.4 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 2H), 3.70 (t, J = 4.8 H, 4H), 2.54 (t, J = 4.8 Hz, 4H).

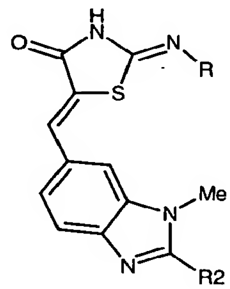
(c) 1-Methyl-2-(4-morpholinylmethyl)-1*H*-benzimidazole-6-carbaldehyde. Following the procedure of Example 9(b), the benzimidazole-6-carbonitrile from Example 46(b) was reduced to the aldehyde in 100% yield. ^{1}H NMR ($CDCl_3$): □10.10 (s, 1H), 7.95 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 1.2, 8.0 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 2H), 3.71 (t, J = 4.8 Hz, 4H), 2.55 (t, J = 4.8 Hz, 4H).

(d) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-{[1-methyl-2-(4-morpholinylmethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

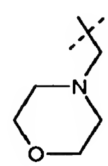
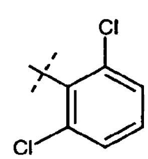
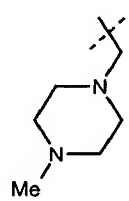
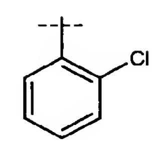
Example	Compound name	Structure	NMR (400 MHz)

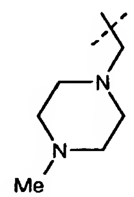
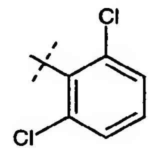
46	(5*Z*)-2-[(2-Chloro-phenyl)-amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]-amino}-1*H*-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.81 (s, 1H), 7.62 (m, 2H), 7.47 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.32 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.18 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.09 (dd, *J* = 0.8, 7.6 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 2H), 3.66 (bs, 4H), 2.50 (bs, 4H)

Examples 47-49



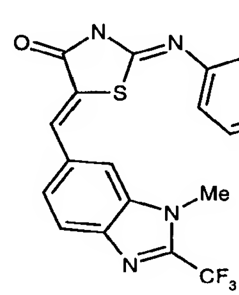
The following compounds were prepared according to the procedure of Example 46, using the requisite amine nucleophile and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R2	R	NMR (400 MHz)
47	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-{[1-methyl-2-(4-morpholinylmethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.68 (m, 1H), 7.60 (m, 2H), 7.40 (m, 3H), 7.09 (m, 1H), 3.90 (s, 3H), 3.82 (s, 2H), 3.67 (bs, 4H), 2.50 (bs, 4H)
48	(5*Z*)-2-[(2-chlorophenyl)amino]-5-({1-methyl-2-[(4-methyl-1-piperazinyl)methyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.90 (m, 1H), 7.87 (s, 1H), 7.80 (m, 1H), 7.64 (m, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 6.8 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.08 (m, 1H), 4.17 (m, 2H), 3.99 (s, 3H), 3.50 (m, 2H), 3.12 (m, 4H), 2.92 (s, 3H), 2.70 (m, 2H)

49	(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-methyl-2-[(4-methyl-1-piperazinyl)methyl]-1*H*-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 7.90 (s, 1H), 7.89 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 8.4 Hz, 1H), 4.14 (s, 2H), 3.98 (s, 3H), 3.50 (m, 2H), 3.12 (m, 4H), 2.91 (s, 3H), 2.68 (m, 2H)

Example 50

(5Z)-2-[(2-Chlorophenyl)amino]-5-{[1-methyl-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one

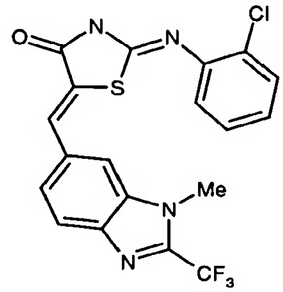


(a) 1-Methyl-2-(trifluoromethyl)-1*H*-benzimidazole-6-carbonitrile. 4-Amino-3-(methylamino)benzonitrile (80 mg, 0.544 mmol) and trifluoroacetic acid (1.1 mL) were heated to reflux for 6 h. Upon cooling, the excess TFA was removed under reduced pressure and sat. aq. $NaHCO_3$ carefully added. A beige solid precipitated, which was filtered, rinsed with H_2O and dried to afford the 2-trifluoromethyl benzimidazole (100 mg, 82%). ^{1}H NMR ($CDCl_3$): □7.98 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.65 (dd, *J* = 1.2, 8.0 Hz, 1H), 4.01 (s, 3H).

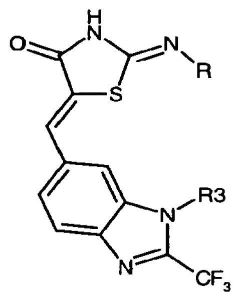
(b) 1-Methyl-2-(trifluoromethyl)-1*H*-benzimidazole-6-carbaldehyde. Following the procedure of Example 9(b), the benzimidazole-6-carbonitrile from Example 50(a) was reduced to the aldehyde in 70% yield. ^{1}H NMR ($CDCl_3$): □10.15 (s, 1H), 8.06 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 4.04 (s, 3H).

(c) (5Z)-2-[(2-Chlorophenyl)amino]-5-{[1-methyl-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

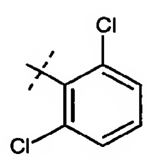
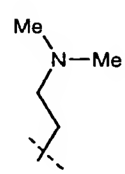
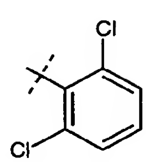
Example	Compound name	Structure	NMR (400 MHz)

50	(5Z)-2-[(2-Chlorophenyl)amino]-5-{[1-methyl-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl]-methylidene}-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.88 (s, 1H), 7.82 (m, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 3.99 (s, 3H)

Examples 51-52

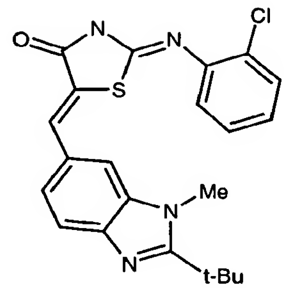


The following compounds were prepared according to the procedure of Example 50, using the requisite diaminobenzonitrile starting material and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R3	R	NMR (400 MHz)
51	(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-methyl-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one	Me		(CD_3OD): 7.90 (s 1H), 7.81 (m, 2H), 7.50 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H)
52	(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-[2-(dimethylamino)ethyl]-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one.			(CD_3OD): 7.90 (m, 3H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 3.59 (m, 2H), 3.06 (m, 2H), 3.02 (s, 6H)

Example 53

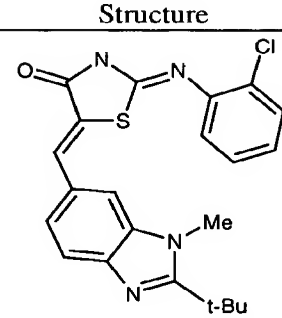
(5Z)-2-[(2-Chlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one



(a) 2-(1,1-Dimethylethyl)-1-methyl-1*H*-benzimidazole-6-carbonitrile. To a mixture of $Cu(OAc)_2$ (800 mg, 4.76 mmol) in AcOH (3.6 mL) and H_2O (1.2 mL), heated to 55 □C, was added 4-amino-3-(methylamino)benzonitrile (70 mg, 0.48 mmol) and pivaldehyde (57 □L, 0.52 mmol). Heating was continued for 2 h, then the solvent was removed under reduced pressure. EtOAc (50 mL) was added, which was washed with sat. aq. $NaHCO_3$. The layers were separated, the aqueous layer extracted with EtOAc (20 mL), and the combined organic layer washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered and concentrated to afford the 2-*t*-butyl benzimidazole (86 mg, 85%). ^1H NMR ($CDCl_3$): □7.78 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, 1H), 7.50 (dd, *J* = 1.2, 8.4 Hz, 1H), 3.95 (s, 3H), 1.58 (s, 9H).

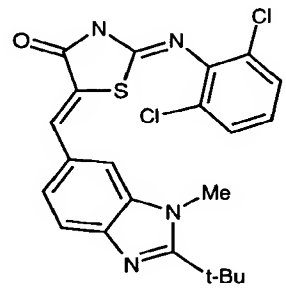
(b) 2-(1,1-Dimethylethyl)-1-methyl-1*H*-benzimidazole-6-carbaldehyde. Following the procedure of Example 9(b), the benzimidazole-6-carbonitrile from Example 53(a) was reduced to the aldehyde in 93% yield. ^1H NMR ($CDCl_3$): □10.08 (s, 1H), 7.89 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 1.2, 8.4 Hz, 1H), 3.99 (s, 3H), 1.59 (s, 9H).

(c) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

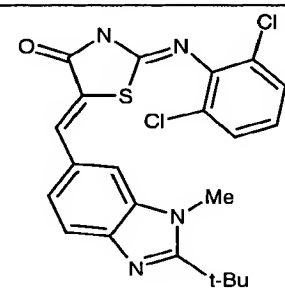
Example	Compound name	Structure	NMR (400 MHz)
53	(5*Z*)-2-[(2-chlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.97 (s, 1H), 7.87 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.32 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.19 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.08 (dd, *J* = 1.2, 7.6 Hz, 1H), 4.17 (s, 3H), 1.66 (s, 9H)

Example 54

(5*Z*)-2-[(2,6-Dichlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one

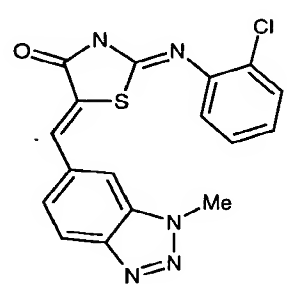


The title compound was prepared according to the procedure of Example 53, except substituting 2-[(2,6-dichlorophenyl)amino]-1,3-thiazol-4(5*H*)-one for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	Structure	NMR (400 MHz)
54	(5*Z*)-2-[(2,6-dichlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1*H*-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5*H*)-one		(CD_3OD): 7.94 (s, 1H), 7.91 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 8.4 Hz, 1H), 4.18 (s, 3H), 1.66 (s, 9H)

Example 55

(5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one

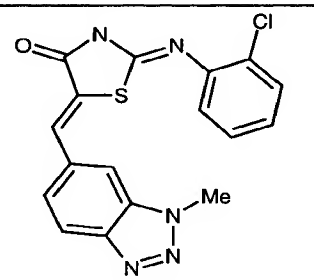


(a) 1-Methyl-1*H*-1,2,3-benzotriazole-6-carbonitrile. To a 0 □C mixture of 4-amino-3-(methylamino)benzonitrile (60 mg, 0.408 mmol) in conc. HCl (0.55 mL) was added $NaNO_2$ (31 mg, 0.449 mmol) in H_2O (0.2 mL). The mixture was allowed to warm to room temperature and stirred for 1 h. After recooling to 0 □C, the mixture was treated with 6N NaOH until basic, the precipitate filtered, rinsed with

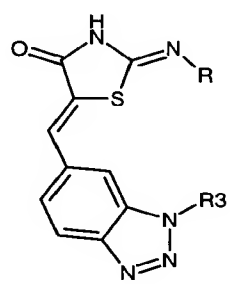
H_2O and dried to afford the benzotriazole nitrile (50 mg, 77%). ^1H NMR ($CDCl_3$): □8.19 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 4.38 (s, 3H).

(b) 1-Methyl-1*H*-1,2,3-benzotriazole-6-carbaldehyde. Following the procedure of Example 9(b), the benzimidazole-6-carbonitrile from Example 55(a) was reduced to the aldehyde in 92% yield. ^1H NMR ($CDCl_3$): □10.20 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.11 (t, *J* = 1.2 Hz, 1H), 7.93 (dd, *J* = 1.2, 8.8 Hz, 1H), 4.41 (s, 3H).

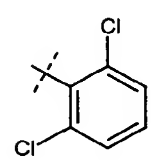
(c) (5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one. Knoevenagel coupling with 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one was accomplished using the procedure of Example 1(e).

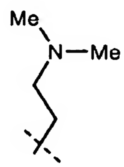
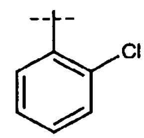
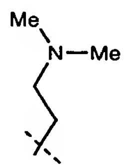
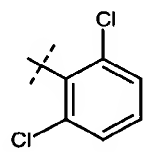
Example	Compound name	Structure	NMR (400 MHz)
55	(5*Z*)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1*H*-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one		(CD_3OD): 8.01 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 2H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.33 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.19 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.32 (s, 3H)

Examples 56-58



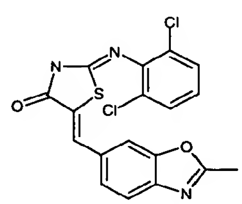
The following compounds were prepared according to the procedure of Example 55, using the requisite diaminobenzonitrile starting material and substituting the appropriate thiazolone for 2-[(2-chlorophenyl)amino]-1,3-thiazol-4(5*H*)-one:

Example	Compound name	R3	R	NMR (400 MHz)
56	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-[(1-methyl-1*H*-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5*H*)-one	Me		(CD_3OD): 8.01 (d, *J* = 8.8 Hz, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 4.32 (s, 3H)

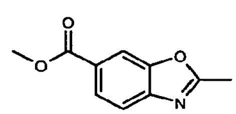
57	(5*Z*)-2-[(2-chlorophenyl) amino]-5-({1-[2-(dimethylamino) ethyl]-1*H*-1,2,3-benzotriazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.10 (d, *J* = 8.8 Hz, 1H), 7.96 (s, 1H), 7.89 (s, 1H), 7.60 (d, *J* = 10.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.19 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.15 (t, *J* = 6.0 Hz, 2H), 3.87 (t, *J* = 5.6 Hz, 2H), 3.01 (s, 6H)
58	(5*Z*)-2-[(2,6-dichlorophenyl) amino]-5-({1-[2-(dimethylamino) ethyl]-1*H*-1,2,3-benzotriazol-6-yl}methylidene)-1,3-thiazol-4(5*H*)-one			(CD_3OD): 8.10 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.91 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 5.16 (t, *J* = 6.0 Hz, 2H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.01 (s, 6H)

Example 59

2-(2,6-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one

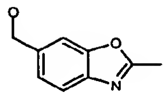


a) <u>2-Methyl-benzooxazole-6-carboxylic acid methyl ester</u>



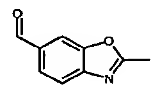
A suspension of methyl 4-amino-3-hydroxy-benzoate (30 g, 0.18 mol) in triethylorthoacetate (90 mL) was heated to 100 °C for 3 hours. Ethanol (150 mL) was added followed by water (50 mL). The reaction mixture was filtered to yield 25 g (72 % yield) of pure 2-methyl-benzooxazole-6-carboxylic acid methyl ester. ^{1}H-NMR ($CDCl_3$): □2.67 (s, 3H), 3.94 (s, 3H), 7.65 (d, 1H, J=8.1 Hz), 8.02 (dd, 1H, J=8.1 Hz, J'=1.5 Hz), 8.15 (d, 1H, J=1.5 Hz). LC MS (m/e) = 192.2 (MH+). Rt = 1.70 min

b) <u>(2-Methyl-benzooxazol-6-yl)-methanol</u>



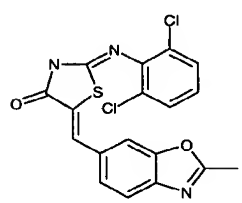
To the solution of 2-methyl-benzooxazole-6-carboxylic acid methyl ester (25 g, 0.13 mol) in THF (500 mL) at –20 °C was added a solution of lithium aluminum hydride (4.81 g, 130 mL of 1 M solution in THF, 0.13 mmol, 1 eq) and the reaction mixture was allowed to warm up to the room temperature overnight. Water (5 mL) followed by 1 M NaOH solution (5 mL) followed by water (15 mL) was added and the reaction mixture was stirred for 15 min at the room temperature. The suspension was filtered, liquid evaporated and purified by column chromatography (1:3 ethyl acetate: dichloromethane) to give 12.5 g (58 % yield) of pure (2-methyl-benzooxazol-6-yl)-methanol. ^{1}H-NMR ($CDCl_3$): □2.64 (s, 3H), 4.82 (s, 2H), 7.29 (d, 1H, J=8 Hz), 7.53 (s, 1H), 7.62 (d, 1H, J=8 Hz). LC MS (m/e) = 164.2 (MH+). Rt = 1.03 min.

c) 2-Methyl-benzooxazole-6-carbaldehyde



To the solution (2-methyl-benzooxazol-6-yl)-methanol (12.5 g, 76 mmol) in dichloromethane (200 mL) was added pyridinium chlorochromate (20 g, 93 mmol, 1.2 eq) and the reaction mixture was stirred for 1 hour at the room temperature. Celite (10 g) was added followed by decolorizing carbon (2 g) and the reaction mixture was filtered after 15 min of stirring. After evaporation the crude product was purified column chromatography (1:10 ethyl acetate: dichloromethane) of give 8.2 g (66 % yield) of pure 2-methyl-benzooxazole-6-carbaldehyde. ^{1}H-NMR ($CDCl_3$): □2.73 (s, 3H), 7.79 (d, 1H, J=8.1 Hz), 7.88 (dd, 1H, J=8.1 Hz, J'=1.2 Hz), 8.03 (d, 1H, J=1.2 Hz), 10.09 (s, 1H). LC MS (m/e) = 162.2 (MH+). Rt = 1.47 min.

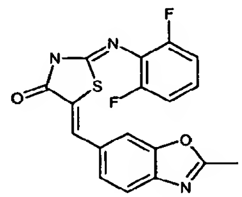
d) 2-(2,6-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one



To the solution of 2-(2,6 dichloro-phenylimino)-thiazolidin-4-one (483 mg, 1.85 mmol) in acetic acid (8 mL) was added 2-methyl-benzooxazole-6-carbaldehyde (300 mg, 1.85 mmol, 1 eq) followed by sodium acetate (0.8 g). The reaction mixture was refluxed for 48 hours and water (10 mL) was added. Solid was filtered and purified by column chromatography (1:5 ethyl acetate:dichloromethane) to give 110 mg (15 % yield) of pure 2-(2,6-dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one. ^{1}H-NMR ($CDCl_3$): □2.69 (s, 3H), 7.12 (t, 1H, J=8.1 Hz), 7.36 (d, 3H, J=7.8 Hz), 7.56 (s, 1H), 7.70 (d, 1H, J=8.1 Hz), 7.88 (s, 1H), 9.69 (s, 1H). LC MS (m/e) = 404.0 (MH+). Rt = 2.36 min.

Example 60.

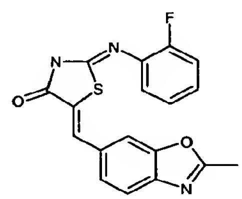
2-(2,6-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one



Following the procedure of example 59 (d), starting from 2-(2,6-difluoro-phenylimino)-thiazolidin-4-one, the title compound was prepared as a yellow solid (82 mg, 22%). ^{1}H-NMR ($CDCl_3$): □2.69 (s, 3H), 7.30 (t, 2H, J=7.9 Hz), 7.15 (m, 1H), 7.41 (d, 1H, J=8.3 Hz), 7.57 (s, 1H), 7.70 (d, 1H, J=8.1 Hz), 7.81 (s, 1H), LC MS (m/e) = 372.0 (MH+). Rt = 2.13 min.

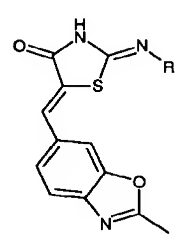
Example 61.

2-(2-Fluoro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one

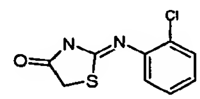
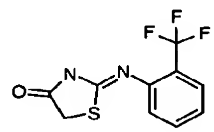
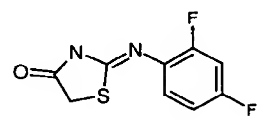
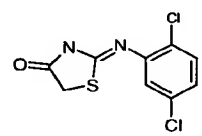
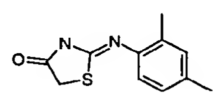
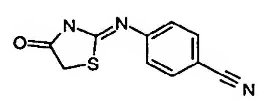
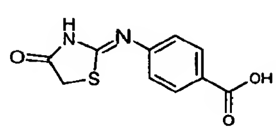
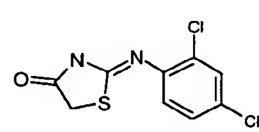


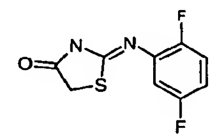
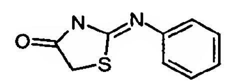
To the solution of 2-(2,6-difluoro-phenylimino)-thiazolidin-4-one (105 mg, 0.5 mmol) in ethanol (5 mL) was added 2-methyl-benzooxazole-6-carbaldehyde (80 mg, 0.5 mmol, 1 eq) followed by piperidine (0.1 mL). The reaction mixture was refluxed for 48 hours and diethyl ether (3 mL) was added. Solid was filtered to give 58 mg (33 % yield) of pure 2-(2-fluoro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one. LC MS (m/e) = 354.2 (MH+). Rt = 2.11 min.

Examples 62-71



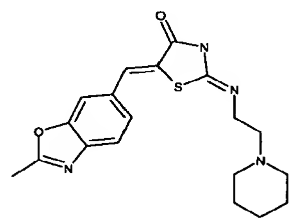
The following compounds were prepared according to the procedure of Example 61, except substituting the appropriately substituted thiazolidinone for 2-(2,6-difluoro-phenylimino)-thiazolidin-4-one.

Example	Product name	Thiazolidinone substituted	LC MS (m/e)	Rt (min)
62	2-(2-Chloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		370.0	2.23
63	2-(2-Trifluromethyl-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		404.0	2.34
64	2-(2,4-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		372.0	2.16
65	2-(2,5-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		404.2	2.46
66	2-(2,4-Dimethyl-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		364.2	2.31
67	2-(4-Cyano-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		361.0	2.07
68	4-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzoic acid		380.0	1.99
69	2-(2,4-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		404.0	2.52

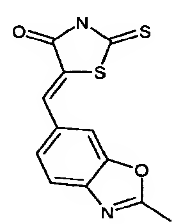
70	2-(2,5-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		372.0	2.20
71	5-(2-Methyl-benzooxazol-6-ylmethylene)-2-phenylimino-thiazolidin-4-one		336.2	2.11

Example 72

5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(2-piperidin-1-yl-ethylimino)-thiazolidin-4-one

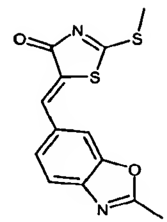


a) 5-(2-Methyl-benzooxazol-6-ylmethylene)-2-thioxo-thiazolidin-4-one



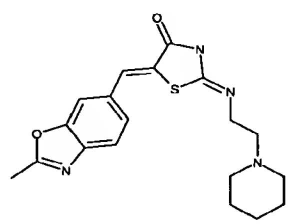
To the solution of rhodanine (1.21 g, 10 mmol) in ethanol (50 mL) was added 2-methyl-benzooxazole-6-carbaldehyde (1.61 mg, 10 mmol, 1 eq) followed by pyridine (1 mL). The reaction mixture was refluxed for 24 hours cooled to the room temperature. Solid was filtered to give 1.3 g (47 % yield) of pure 5-(2-methyl-benzooxazol-6-ylmethylene)-2-thioxo-thiazolidin-4-one. ^{1}H-NMR (DMSO): □2.67 (s, 3H), 2.85 (s, 3H), 7.66 (dd, 1H, J=8.3 Hz, J'=1.7 Hz), 7.82 (d, 1H, J=8.3 Hz), 8.00 (s, 1H), 8.02 (d, 1H, J=1.7 Hz). LC MS (m/e) = 277.0 (MH+). Rt = 2.02 min.

b) 5-(2-Methyl-benzooxazol-6-ylmethylene)-2-methylsulfanyl-thiazol-4-one



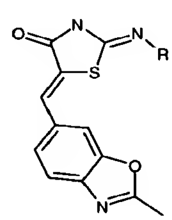
To the solution of 5-(2-methyl-benzooxazol-6-ylmethylene)-2-thioxo-thiazolidin-4-one (200 mg, 0.72 mmol) in ethanol (5 mL) was added diisopropyl ethyl amine (0.185 mL, 1.44 mmol, 2 eq) followed by iodomethane (0.216 mL, 3.5 mmol, 5 eq). The reaction mixture was stirred overnight, then filtered. Solid was washed with cold ethanol to give 193 mg (92 % yield) of pure 5-(2-methyl-benzooxazol-6-ylmethylene)-2-methylsulfanyl-thiazol-4-one. ^{1}H-NMR (DMSO): □2.67 (s, 3H), 7.59 (dd, 1H, J=8.3 Hz, J'=1.5 Hz), 7.80 (s, 1H), 7.82 (d, 1H, J=8.3 Hz), 7.96 (d, 1H, J=1.5 Hz). LC MS (m/e) = 291.0 (MH+). Rt = 2.41 min.

c) 5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(2-piperidin-1-yl-ethylimino)-thiazolidin-4-one

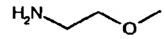
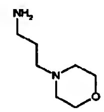
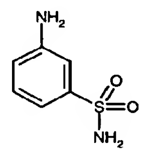
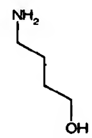
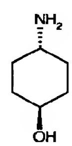
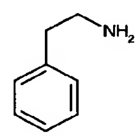
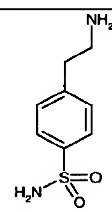
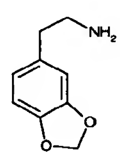


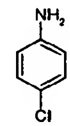
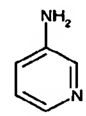
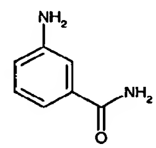
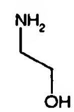
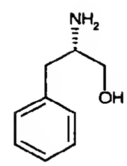
To the solution of 5-(2-methyl-benzooxazol-6-ylmethylene)-2-methylsulfanyl-thiazol-4-one (40 mg, 0.14 mmol) in ethanol (3 mL) was added 2-piperidin-1-yl-ethylamine (25 mg, 0.2 mmol, 1.4 eq) and the reaction mixture was heated under reflux for 24 hours. Diethyl ether (3 mL) was added and product isolated by filtration to give 27 mg (53 % yield) of pure 5-(2-methyl-benzooxazol-6-ylmethylene)-2-(2-piperidin-1-yl-ethylimino)-thiazolidin-4-one. LC MS (m/e) = 371.0 (MH+). Rt = 1.40 min.

Examples 73-85



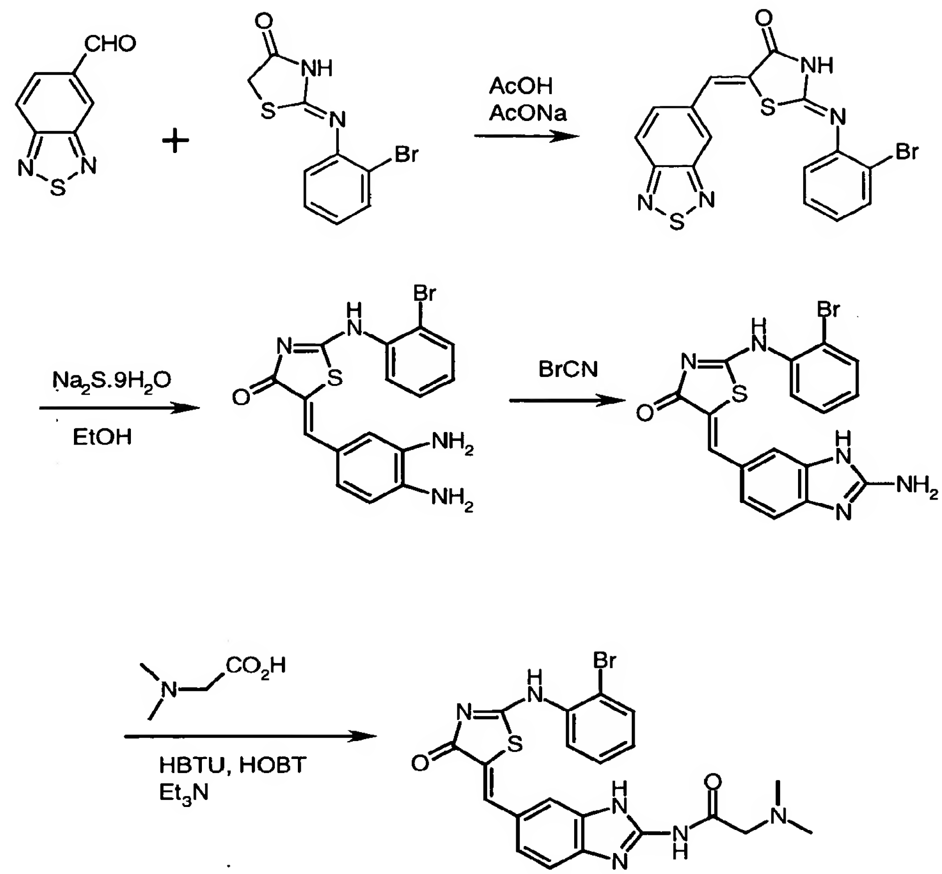
The following compounds were prepared according to the procedure of Example 72 (c), except substituting the appropriate amine listed below for 2-piperidin-1-yl-ethylamine.

Example	Product name	Amine used	LC MS (m/e)	Rt (min)
73	2-(2-Methoxy-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		318.0	1.52
74	5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(3-morpholin-4-yl-propylimino)-thiazolidin-4-one		387.2	1.31
75	3-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzenesulfonamide		415.2	1.68
76	2-(4-Hydroxy-butylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		332.2	1.49
77	2-(trans-4-Hydroxy-cyclohexylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		358.0	1.45
78	5-(2-Methyl-benzooxazol-6-ylmethylene)-2-phenethylimino-thiazolidin-4-one		363.8	2.00
79	4-{2-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-ethyl}-benzenesulfonamide		443.2	1.63
80	2-(2-Benzo[1,3]dioxol-5-yl-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		408.2	1.97

81	2-(4-Chloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		370.0	2.31
82	5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(pyridin-3-ylimino)-thiazolidin-4-one		337.2	1.40
83	3-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzamide		379.2	1.61
84	2-(2-Hydroxy-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		304.0	1.33
85	2-(1-Hydroxymethyl-2-phenyl-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one		394.2	1.76

Example 86

N-{6-[2-(2-Bromo-phenylimino)-4-oxo-thiazolidin-5-ylidenemethyl]-1H-benzoimidazol-2-yl}-2-dimethylamino-acetamide



a. 5-Benzo[1,2,5]thiadiazol-5-ylmethylene-2-(2-bromophenylimino)-thiazolidin-4-one

A mixture of benzo[1,2,5]thiadiazole-5-carbaldehyde (70 mg, 0.43 mmol), (2-bromophenylimino)-thiazolidin-4-one (110 mg, 0.40 mmol), AcONa (100 mg) in AcOH (2 mL) was heated to reflux at 120 degree for 48 hours. After cooling, a small portion of water was added until the solid forms. It was filtered and washed with MeOH, followed by desiccation *in vacuo* to afford a target product (104 mg, 0.25 mmol). ^1H NMR (DMSO-d_6) δ 7.15 (m, 2H), 7.43 (t, 1H), 7.71 (d, 1H), 7.83 (dd, 1H), 7.89 (s, 1H), 8.16 (d, 1H), 8.22 (s, 1H), 12.83 (sbr, 1H) : LC/MS: m/z 417 (M), 419 (M+2)

b. 2-(2-Bromo-phenylamino)-5-(3,4-diamino-benzylidene)-thiazol-4-one

A mixture 5-benzo[1,2,5]thiadiazol-5-ylmethylene-2-(2-bromophenylimino)-thiazolidin-4-one (380 mg) and Na_2S-$9H_2O$ (600 mg) in ethanol was irradiated by a microwave reactor at 120 C° for 5 hours. The mixture was poured onto aq.NH_4Cl and the formed orange precipitate was filtrated. Washing with H_2O and subsequent desiccation gave 290 mg of the title product. ^1H NMR (DMSO-d_6) δ 4.68 (sbr, 2H), 5.30 (s, 2H), 6.44-6.55 (m, 3H), 7.04 (m, 2H), 7.29 (s, 1H), 7.33 (t, 1H), 7.61 (d, 1H): LC/MS: m/z 389 (M), 391 (M+2).

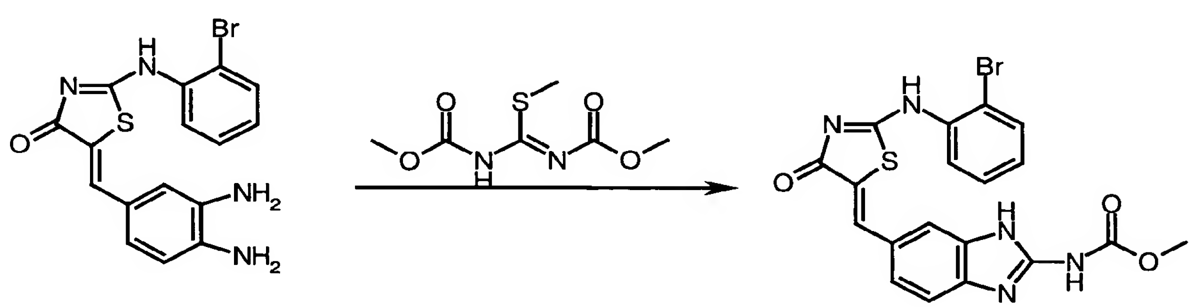
c. 5-(2-Amino-3H-benzoimidazol-5-ylmethylene)-2-(2-bromo-phenylimino)-thiazolidin-4-one

A mixture of 2-(2-bromo-phenylamino)-5-(3,4-diamino-benzylidene)-thiazol-4-one (130 mg) and BrCN (120 mg) in methanol (1.5 ml) was heated at 60 C° for 6h. Treatment with aq. NaOH yielded a precipitate, which then is purified by prep LC-MS to afford the title product (30 mg). ^{1}H NMR (DMSO-d_6) δ 7.07-7.20 (m, 5H), 7.40 (t, 1H), 7.64 (s, 1H), 7.67 (d, 1H): LC/MS: m/z 414 (M), 416 (M+2)

d. N-{6-[2-(2-Bromo-phenylimino)-4-oxo-thiazolidin-5-ylidenemethyl]-1H-benzoimidazol-2-yl}-2-dimethylamino-acetamide

A mixture of 5-(2-amino-3H-benzoimidazol-5-ylmethylene)-2-(2-bromo-phenylimino)-thiazolidin-4-one (40 mg), dimethylaminoacetic acid (13 mg), HBTU (45 mg), and triethylamine (25 mg) in dry DMF (1 ml) was stirred at rt for 6 hours. It was washed with water and the formed yellowish solid was collected by filtration. Prep LC-MS purification afforded the title product (10 mg). ^{1}HNMR (DMSO-d_6) δ 2.30 (s, 6H), 3.24 (s, 2H), 7.10 (m, 2H), 7.29 (m, 1H), 7.39 (m, 1H), 7.46 (m, 1H), 7.63-7.68 (m, 3H): LC/MS: m/z 500 (M+1)

Example 88
Methyl (5-{(Z)-[2-[(2-bromophenyl)amino]-4-oxo-1,3-thiazol-5(4H)-ylidene]methyl}-1H-benzimidazol-2-yl)carbamate



A mixture of 2-(2-bromo-phenylamino)-5-(3,4-diamino-benzylidene)-thiazol-4-one (88 mg, 0.23 mmol) and 1,3-bis(methoxycarbonyl)methyl-2-thiopsuedourea (46 mg, 0.23 mmol) in dry methanol (1.5 mL) was heated overnight at 60 C° with a air-cooling condenser. The formed yellowish solid was filtered and then washed with H_2O and MeOH to provide the title product (39 mg). ^{1}H NMR (DMSO-d_6) 3.75 (s, 3H), 7.12-7.16 (m, 2H), 7.28 (d, 1H), 7.41-7.46 (m, 2H), 7.57 (s, 1H), 7.71 (d, 1H), 7.74 (s, 1H), 12.0 (brs,

2H).

Biological Methods and Data

As demonstrated by the representative compounds of the present invention in Table 1, the compounds of the present invention have valuable pharmacological properties due to their potent ability to inhibit the hYAK3 kinase enzyme.

Substrate phosphorylation assays were carried out as follows:

YAK3 Scintillation Proximity Assays Using Ser164 of Myelin Basic Protein as the phosphoacceptor

The source of Ser164 substrate peptide The biotinylated Ser164, S164A peptide(Biotinyl-LGGRDSRAGS*PMARR-OH), sequence derived from the C-terminus of bovine myelin basic protein (MBP) with Ser162 substituted as Ala162, was purchased from California Peptide Research Inc. (Napa, CA), and its purity was determined by HPLC. Phosphorylation occurs at position 164 (marked S* above). The calculated molecular mass of the peptide was 2166 dalton. Solid sample was dissolved at 10 mM in DMSO, aliquoted, and stored at –20 °C until use.

The source of enzyme:
hYAK3: Glutathione-S-Transferase (GST)-hYak3-His6 containing amino acid residues 124-526 of human YAK3 (aa 124-526 of SEQ ID NO 2. in US patent no. 6,323,318) was purified from baculovirus expression system in Sf9 cells using Glutathione Sepharose 4B column chromatography followed by Ni-NTA-Agarose column chromatography. Purity greater than 65% typically was achieved. Samples, in 50 mM Tris, 150 mM NaCl, 10%glycerol, 0.1% Triton, 250 mM imidazole, 10 mM β-mercapto ethanol, pH 8.0. were stored at –80 °C until use.

Kinase assay of purified hYAK3: Assays were performed in 96 well (Costar, Catalog No. 3789) or 384 well plates (Costar, Catalog No. 3705). Reaction (in 20, 25, or 40 μl volume) mix contained in final concentrations 25 mM Hepes buffer, pH 7.4; 10 mM $MgCl_2$; 10 mM β-mercapto ethanol; 0.0025% Tween-20; 0.001 mM ATP, 0.1 □Ci of [□-^{33}P]ATP; purified hYAK3 (7-14 ng/assay; 4 nM final); and 4 μM Ser164 peptide. Compounds, titrated in DMSO, were evaluated at concentrations ranging from 50 μM to 0.5 nM. Final assay

concentrations of DMSO did not exceed 5%, resulting in less than 15% loss of YAK3 activity relative to controls without DMSO. Reactions were incubated for 2 hours at room temperature and were stopped by a 75 ul addition of 0.19 μg Streptavidin Scintillation Proximity beads (Amersham Pharmacia Biotech, Catalog No. RPNQ 0007) in PBS, pH 7.4, 10 mM EDTA, 0.1% Triton X-100, 1 mM ATP. Under the assay conditions defined above, the K_m(apparent) for ATP was determined to be 7.2 +/- 2.4 μM.

Table 1

Compounds from example nos.	pIC_{50} values
59	+++
58	++
53	+

Legend

pIC_{50} values	Symbol
8.99 – 8	+++
7.99 – 7	++
6.99 – 6	+

$pIC_{50} = -\log_{10}(IC_{50})$

Utility of the Present Invention

The above biological data clearly shows that the compounds of formula I are useful for treating or preventing disease states in which hYAK3 proteins are implicated, especially diseases of the erythroid and hematopoietic systems, including but not limited to, anemias due to renal insufficiency or to chronic disease, such as autoimmunity, HIV, or cancer, and drug-induced anemias, myelodysplastic syndrome, aplastic anemia, myelosuppression, and cytopenia.

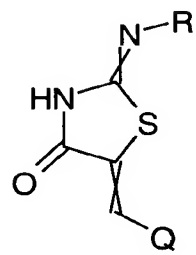
The compounds of formula I are especially useful in treating diseases of the hematopoietic system, particularly anemias. Such anemias include an anemia selected from the group comprising: aplastic anemia and myelodysplastic syndrome. Such anemias also include those wherein the anemia is a consequence of a primary disease selected from the group

consisting of: cancer, leukemia and lymphoma. Such anemias also include those wherein the anemia is a consequence of a primary disease selected from the group consisting of: renal disease, failure or damage. Such anemias include those wherein the anemia is a consequence of chemotherapy or radiation therapy, in particular wherein the chemotherapy is chemotherapy for cancer or AZT treatment for HIV infection. Such anemias include those wherein the anemia is a consequence of a bone marrow transplant or a stem cell transplant. Such anemias also include anemia of newborn infants. Such anemias also include those which are a consequence of viral, fungal, microbial or parasitic infection.

The compounds of formula I are also useful for enhancing normal red blood cell numbers. Such enhancement is desirable for a variety of purposes, especially medical purposes such as preparation of a patient for transfusion and preparation of a patient for surgery.

What is claimed is:

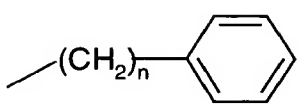
1. A compound of the formula I, or a salt, solvate, or a physiologically functional derivative thereof



I

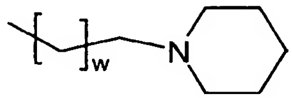
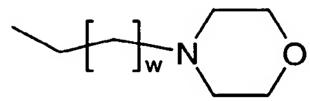
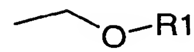
in which

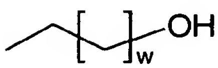
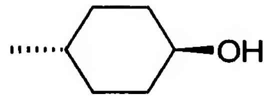
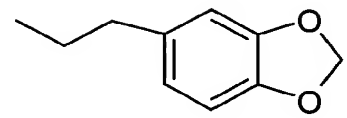
R is

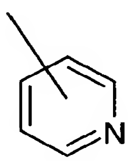
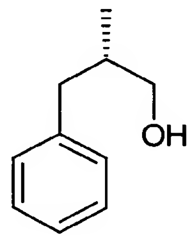


in which the phenyl radical is optionally and independently substituted with up to three halogen, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-CF_3$, -CN, $-CO_2H$, $-SO_2NH_2$, $-CONH_2$; or

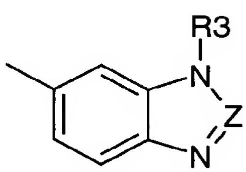
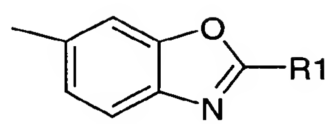
R is a radical of the formula

 ,  ,  ,

 ,  , 

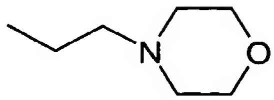
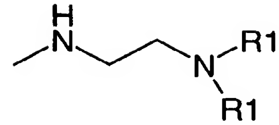
 ,  ; and

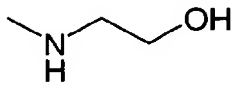
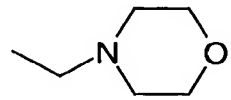
Q is a radical of the formula

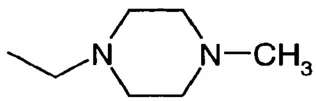
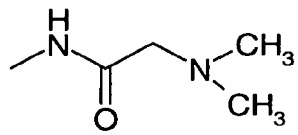
 or 

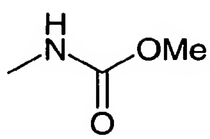
in which Z is N or C-R2;

wherein R2 is hydrogen, $-NH_2$, $-C_{1-6}$alkyl, $-CF_3$, or a radical of the formula

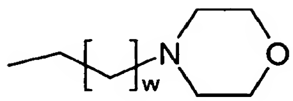
 ,  ,

 ,  ,

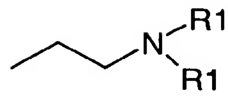
 ,  , or

 ; and

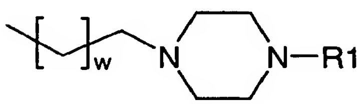
R3 is -C_{1-6} alkyl, or a radical of the formula



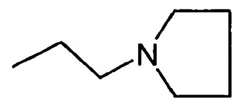
,



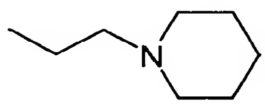
,



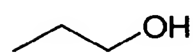
,



,



, or

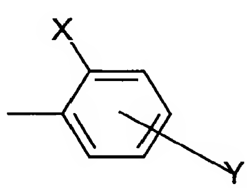


; and

n equals zero to two;
w equals one to two; and
R1 is $-C_{1-6}$alkyl.

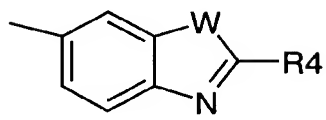
2. A compound of claim 1 in which R is phenyl optionally and independently substituted with up to three halogen, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-CF_3$, -CN, $-CO_2H$, $-SO_2NH_2$, $-CONH_2$.

3. A compound of claim 2 in which R is



in which X is halogen or CF3; and Y is hydrogen, halogen, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-CF_3$, -CN, $-CO_2H$, $-SO_2NH_2$, $-CONH_2$.

4. A compound of claim 3 in which Q is



in which R4 is methyl or hydrogen, and W is O or N-R1, in which R1 is -C_{1-6}alkyl.

5. A method of inhibiting hYAK3 in a mammal; comprising, administering to the mammal a therapeutically effective amount of a compound of claim 1, 2, 3, or 4, or a salt, solvate, or a physiologically functional derivative thereof

6. A method of treating or preventing diseases of the erythroid and hematopoietic systems, caused by the hYAK3 imbalance or inappropriate activity; comprising, administering to a mammal a therapeutically effective amount of a compound of claim 1, 2, 3, or 4, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

7. A method of claim 6 in which diseases of the erythroid and hematopoietic systems are selected from the group consisting of: anemia, aplastic anemia, myelodysplastic syndrome, myelosuppression, and cytopenia.

8. A method of treating or preventing diseases selected from the group consisting of: anemia, aplastic anemia, myelodysplastic syndrome, myelosuppression, and cytopenia; comprising, administering to a mammal a therapeutically effective amount of a compound of claim 1, 2, 3 or 4, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

9. A pharmaceutical composition including a therapeutically effective amount of a compound claim 1, 2, 3, or 4, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

10. A compound selected from the group consisting of:

(5Z)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-difluorophenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;

(5Z)-2-[(2,4-dimethylphenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-2-{[2-(methyloxy)phenyl]amino}-1,3-thiazol-4(5H)-one;
(5Z)-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-2-{[2-(trifluoromethyl)phenyl]amino}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,4-difluorophenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chloro-4-fluorophenyl)amino]-5-[(1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-Chlorophenyl)-amino]-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)-methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-difluorophenyl)amino]-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)methylidene]-2-[(2,4-dimethylphenyl)amino]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,4-difluorophenyl)amino]-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chloro-4-fluorophenyl)amino]-5-[(1,2-dimethyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-Chlorophenyl)-amino]-5-({1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-6-yl}-methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chloro-4-fluorophenyl)amino]-5-({1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,4-difluorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-5-({1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-2-(phenylamino)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[2-(diethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(diethylamino)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[3-(4-methyl-1-piperazinyl)propyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[3-(4-methyl-1-piperazinyl)propyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-

yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-difluorophenyl)amino]-5-({1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-Chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,4-difluorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-5-({1-[2-(dimethylamino)ethyl]-2-methyl-1H-benzimidazol-6-yl}methylidene)-2-(phenylamino)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-(2-hydroxyethyl)-2-methyl-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-difluorophenyl)amino]-5-({2-methyl-1-[2-(1-piperidinyl)ethyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,4-difluorophenyl)amino]-5-[(1-methyl-2-{[2-(4-morpholinyl)ethyl]amino}-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-[(2-{[2-(dimethylamino)ethyl]amino}-1-methyl-1H-benzimidazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({2-[(2-hydroxyethyl)amino]-1-methyl-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-{[1-methyl-2-(4-morpholinylmethyl)-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-methyl-2-(4-morpholinylmethyl)-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-({1-methyl-2-[(4-methyl-1-piperazinyl)methyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-methyl-2-[(4-methyl-1-piperazinyl)methyl]-1H-benzimidazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-Chlorophenyl)-amino]-5-{[1-methyl-2-(trifluoromethyl)-1H-benzimidazol-6-yl]-methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-methyl-2-(trifluoromethyl)-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[1-[2-(dimethylamino)ethyl]-2-(trifluoromethyl)-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-chlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-{[2-(1,1-dimethylethyl)-1-methyl-1H-benzimidazol-6-yl]methylidene}-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2-Chlorophenyl)amino]-5-[(1-methyl-1H-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-[(1-methyl-1H-1,2,3-benzotriazol-6-yl)methylidene]-1,3-thiazol-4(5H)-one;

(5Z)-2-[(2-chlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1H-1,2,3-benzotriazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
(5Z)-2-[(2,6-dichlorophenyl)amino]-5-({1-[2-(dimethylamino)ethyl]-1H-1,2,3-benzotriazol-6-yl}methylidene)-1,3-thiazol-4(5H)-one;
2-(2,6-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one;
2-(2,6-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one;
2-(2-Fluoro-phenylimino)-5-(2-methyl-benzooxazol-6-yl-methylene)-thiazolidin-4-one;
2-(2-Chloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(2-Trifluromethyl-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(2,4-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(2,5-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(2,4-Dimethyl-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(4-Cyano-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
4-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzoic acid;
2-(2,4-Dichloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(2,5-Difluoro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
5-(2-Methyl-benzooxazol-6-ylmethylene)-2-phenylimino-thiazolidin-4-one;
5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(2-piperidin-1-yl-ethylimino)-thiazolidin-4-one;
2-(2-Methoxy-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(3-morpholin-4-yl-propylimino)-thiazolidin-4-one;
3-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzenesulfonamide;
2-(4-Hydroxy-butylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(trans-4-Hydroxy-cyclohexylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
5-(2-Methyl-benzooxazol-6-ylmethylene)-2-phenethylimino-thiazolidin-4-one;
4-{2-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-ethyl}-benzenesulfonamide;
2-(2-Benzo[1,3]dioxol-5-yl-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(4-Chloro-phenylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
5-(2-Methyl-benzooxazol-6-ylmethylene)-2-(pyridin-3-ylimino)-thiazolidin-4-one;
3-[5-(2-Methyl-benzooxazol-6-ylmethylene)-4-oxo-thiazolidin-2-ylideneamino]-benzamide;
2-(2-Hydroxy-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
2-(1-Hydroxymethyl-2-phenyl-ethylimino)-5-(2-methyl-benzooxazol-6-ylmethylene)-thiazolidin-4-one;
N-{6-[2-(2-Bromo-phenylimino)-4-oxo-thiazolidin-5-ylidenemethyl]-1H-benzoimidazol-2-yl}-2-dimethylamino-acetamide; and
Methyl (5-{(Z)-[2-[(2-bromophenyl)amino]-4-oxo-1,3-thiazol-5(4H)-ylidene]methyl}-1H-benzimidazol-2-yl)carbamate.

ABSTRACT

This invention relates to newly identified compounds for inhibiting hYAK3 proteins and methods for treating diseases associated with the imbalance or inappropriate activity of hYAK3 proteins.